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(54) Title: PYRAZOLOPYRIMIDINES AS CYCLIN DEPENDENT KINASE INHIBITORS

(57) Abstract: In its many embodiments, the present invention provides a novel class of pyrazolo[1,5-a]pyrimidine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions containing one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with the CDKs using such compounds or pharmaceutical compositions.

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## PYRAZOLOPYRIMIDINES AS CYCLIN DEPENDENT KINASE INHIBITORS

Field of the Invention

The present invention relates to pyrazolo[1,5-a]pyrimidine compounds useful as protein kinase inhibitors, pharmaceutical compositions containing the compounds, and methods of treatment using the compounds and compositions to treat diseases such as, for example, cancer, inflammation, arthritis, viral diseases, neurodegenerative diseases such as Alzheimer's disease, cardiovascular diseases, and fungal diseases. This application claims benefit of priority from U.S. provisional patent application Serial No. 60/408,182 filed September 4, 2002.

10

Background of the Invention

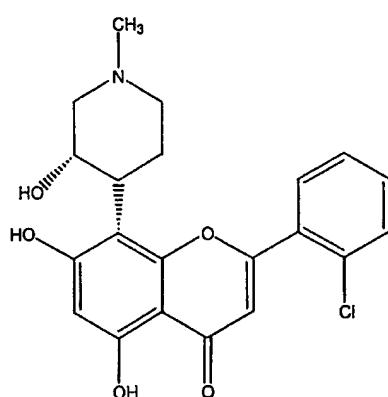
The cyclin-dependent kinases (CDKs) are serine/threonine protein kinases, which are the driving force behind the cell cycle and cell proliferation. Individual CDK's, such as, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 and CDK7, CDK8 and the like, perform distinct roles in cell cycle progression and can be classified as either G1, S, or G2M phase enzymes. Uncontrolled proliferation is a hallmark of cancer cells, and misregulation of CDK function occurs with high frequency in many important solid tumors. CDK2 and CDK4 are of particular interest because their activities are frequently misregulated in a wide variety of human cancers. CDK2 activity is required for progression through G1 to the S phase of the cell cycle, and CDK2 is one of the key components of the G1 checkpoint. Checkpoints serve to maintain the proper sequence of cell cycle events and allow the cell to respond to insults or to proliferative signals, while the loss of proper checkpoint control in cancer cells contributes to tumorigenesis. The CDK2 pathway influences tumorigenesis at the level of tumor suppressor function (e.g. p52, RB, and p27) and oncogene activation (cyclin E). Many reports have demonstrated that both the coactivator, cyclin E, and the inhibitor, p27, of CDK2 are either over – or underexpressed, respectively, in breast, colon, nonsmall cell lung, gastric, prostate, bladder, non-Hodgkin's lymphoma, ovarian, and other cancers. Their altered expression has been shown to correlate with increased

CDK2 activity levels and poor overall survival. This observation makes CDK2 and its regulatory pathways compelling targets for the development years, a number of adenosine 5'-triphosphate (ATP) competitive small organic molecules as well as peptides have been reported in the literature as CDK inhibitors for the

5 potential treatment of cancers. U.S. 6,413,974, col. 1, line 23- col. 15, line 10 offers a good description of the various CDKs and their relationship to various types of cancer.

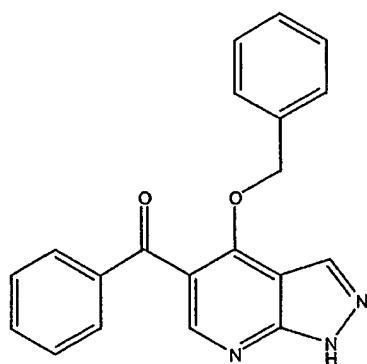
CDK inhibitors are known. For example, flavopiridol (Formula I) is a nonselective CDK inhibitor that is currently undergoing human clinical trials, A. M.

10 Sanderowicz *et al*, *J. Clin. Oncol.* (1998) 16, 2986-2999.



Formula I

Other known inhibitors of the CDKs include, for example, olomoucine (J. Vesely *et al*, *Eur. J. Biochem.*, (1994) 224, 771-786) and roscovitine (I. Meijer *et al*, *Eur. J. Biochem.*, (1997) 243, 527-536). U.S. 6,107,305 describes certain pyrazolo[3,4-b] pyridine compounds as CDK inhibitors. An illustrative compound from the '305 patent has the Formula II:



## Formula II

K. S. Kim *et al*, *J. Med. Chem.* 45 (2002) 3905-3927 and WO 02/10162 disclose certain aminothiazole compounds as CDK inhibitors.

Pyrazolopyrimidines are known. For Example, WO92/18504, 5 WO02/50079, WO95/35298, WO02/40485, EP94304104.6, EP0628559 (equivalent to US Patents 5,602,136, 5,602,137 and 5,571,813), U.S. 6,383,790, *Chem. Pharm. Bull.*, (1999) 47 928, *J. Med. Chem.*, (1977) 20, 296, *J. Med. Chem.*, (1976) 19 517 and *Chem. Pharm. Bull.*, (1962) 10 620 disclose various pyrazolopyrimidines.

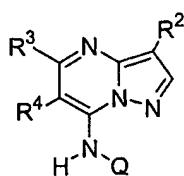
10 There is a need for new compounds, formulations, treatments and therapies to treat diseases and disorders associated with CDKs. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of such diseases and disorders.

15

Summary of the Invention

In its many embodiments, the present invention provides a novel class of pyrazolo[1,5-a]pyrimidine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical 20 formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more diseases associated with the CDKs using such compounds or pharmaceutical compositions.

In one aspect, the present application discloses a compound, or 25 pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula III:



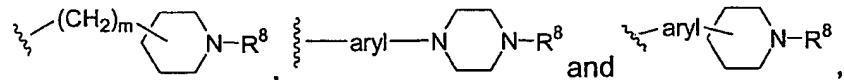
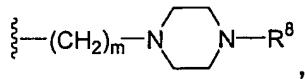
Formula III

wherein:

Q is selected from the group consisting of  $-\text{S}(\text{O}_2)\text{NR}^6\text{R}^7$ -,  $-\text{C}(\text{O})\text{NR}^6\text{R}^7$ - and  $-\text{C}(\text{O})\text{OR}^7$ ;

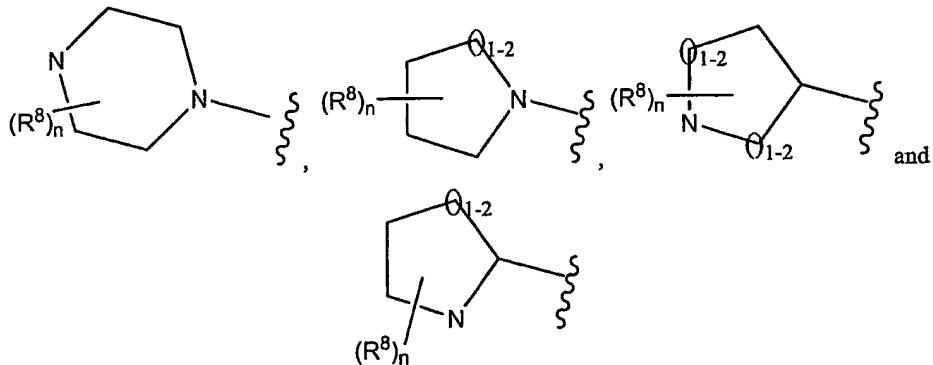
$\text{R}^2$  is selected from the group consisting of  $\text{R}^9$ , alkyl, alkynyl, alkynylalkyl, cycloalkyl,  $-\text{CF}_3$ ,  $-\text{C}(\text{O}_2)\text{R}^6$ , aryl, arylalkyl, heteroarylalkyl, heterocyclyl, alkyl

5 substituted with 1-6  $\text{R}^9$  groups which can be the same or different and are independently selected from the list of  $\text{R}^9$  shown later below,



10 wherein the aryl in the above-noted definitions for  $\text{R}^2$  can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, CN,  $-\text{OR}^5$ ,  $\text{SR}^5$ ,  $-\text{S}(\text{O}_2)\text{R}^6$ ,  $-\text{S}(\text{O}_2)\text{NR}^5\text{R}^6$ ,  $-\text{NR}^5\text{R}^6$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^6$ ,  $\text{CF}_3$ , alkyl, aryl and  $\text{OCF}_3$ ;

15  $\text{R}^3$  is selected from the group consisting of H, halogen, alkyl, alkynyl,  $-\text{C}(\text{O})\text{NR}^5\text{R}^6$ ,  $-\text{C}(\text{O})\text{OR}^4$ ,  $-\text{NR}^5\text{R}^6$ , cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl,



20 wherein each of said alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl for  $\text{R}^3$  and the heterocyclyl moieties whose structures are shown immediately above for  $\text{R}^3$  can be substituted or optionally independently substituted with one or more moieties

which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF<sub>3</sub>, CN, -OCF<sub>3</sub>, -(CR<sup>4</sup>R<sup>5</sup>)<sub>n</sub>OR<sup>5</sup>, -OR<sup>5</sup>, -NR<sup>5</sup>R<sup>6</sup>, -(CR<sup>4</sup>R<sup>5</sup>)<sub>n</sub>NR<sup>5</sup>R<sup>6</sup>, -C(O<sub>2</sub>)R<sup>5</sup>, -C(O)R<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -SR<sup>6</sup>, -S(O<sub>2</sub>)R<sup>6</sup>, -S(O<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>5</sup>)S(O<sub>2</sub>)R<sup>7</sup>, -N(R<sup>5</sup>)C(O)R<sup>7</sup> and

5 -N(R<sup>5</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>;

R<sup>4</sup> is H, halo or alkyl;

R<sup>5</sup> is H or alkyl;

R<sup>6</sup> is selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl,

10 wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, heterocyclylalkyl, CF<sub>3</sub>, OCF<sub>3</sub>, CN, -OR<sup>5</sup>, -NR<sup>5</sup>R<sup>10</sup>,

15 -N(R<sup>5</sup>)Boc, -(CR<sup>4</sup>R<sup>5</sup>)<sub>n</sub>OR<sup>5</sup>, -C(O<sub>2</sub>)R<sup>5</sup>, -C(O)R<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>10</sup>, -SO<sub>3</sub>H, -SR<sup>10</sup>, -S(O<sub>2</sub>)R<sup>7</sup>, -S(O<sub>2</sub>)NR<sup>5</sup>R<sup>10</sup>, -N(R<sup>5</sup>)S(O<sub>2</sub>)R<sup>7</sup>, -N(R<sup>5</sup>)C(O)R<sup>7</sup> and -N(R<sup>5</sup>)C(O)NR<sup>5</sup>R<sup>10</sup>;

R<sup>10</sup> is selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl, wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl,

20 wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, heterocyclylalkyl, CF<sub>3</sub>, OCF<sub>3</sub>, CN, -OR<sup>5</sup>, -NR<sup>4</sup>R<sup>5</sup>, -N(R<sup>5</sup>)Boc, -(CR<sup>4</sup>R<sup>5</sup>)<sub>n</sub>OR<sup>5</sup>, -C(O<sub>2</sub>)R<sup>5</sup>, -C(O)NR<sup>4</sup>R<sup>5</sup>, -C(O)R<sup>5</sup>, -SO<sub>3</sub>H, -SR<sup>5</sup>,

25 -S(O<sub>2</sub>)R<sup>7</sup>, -S(O<sub>2</sub>)NR<sup>4</sup>R<sup>5</sup>, -N(R<sup>5</sup>)S(O<sub>2</sub>)R<sup>7</sup>, -N(R<sup>5</sup>)C(O)R<sup>7</sup> and -N(R<sup>5</sup>)C(O)NR<sup>4</sup>R<sup>5</sup>;

or optionally (i) R<sup>5</sup> and R<sup>10</sup> in the moiety -NR<sup>5</sup>R<sup>10</sup>, or (ii) R<sup>5</sup> and R<sup>6</sup> in the moiety -NR<sup>5</sup>R<sup>6</sup>, may be joined together to form a cycloalkyl or heterocyclyl moiety, with each of said cycloalkyl or heterocyclyl moiety being unsubstituted or optionally independently being substituted with one or more R<sup>9</sup> groups;

30 R<sup>7</sup> is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, cycloalkyl,

heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl,  $\text{CF}_3$ ,  $\text{OCF}_3$ ,  $\text{CN}$ ,  $-\text{OR}^5$ ,  $-\text{NR}^5\text{R}^{10}$ ,  $-\text{CH}_2\text{OR}^5$ ,

5  $-\text{C}(\text{O}_2)\text{R}^5$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{10}$ ,  $-\text{C}(\text{O})\text{R}^5$ ,  $-\text{SR}^{10}$ ,  $-\text{S}(\text{O}_2)\text{R}^{10}$ ,  $-\text{S}(\text{O}_2)\text{NR}^5\text{R}^{10}$ ,

$-\text{N}(\text{R}^5)\text{S}(\text{O}_2)\text{R}^{10}$ ,  $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{R}^{10}$  and  $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{NR}^5\text{R}^{10}$ ;

$\text{R}^8$  is selected from the group consisting of  $\text{R}^6$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{10}$ ,  
 $-\text{S}(\text{O}_2)\text{NR}^5\text{R}^{10}$ ,  $-\text{C}(\text{O})\text{R}^7$  and  $-\text{S}(\text{O}_2)\text{R}^7$ ;

$\text{R}^9$  is selected from the group consisting of halogen,  $\text{CN}$ ,  $-\text{NR}^5\text{R}^{10}$ ,

10  $-\text{C}(\text{O}_2)\text{R}^6$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{10}$ ,  $-\text{OR}^6$ ,  $-\text{SR}^6$ ,  $-\text{S}(\text{O}_2)\text{R}^7$ ,  $-\text{S}(\text{O}_2)\text{NR}^5\text{R}^{10}$ ,  $-\text{N}(\text{R}^5)\text{S}(\text{O}_2)\text{R}^7$ ,  
 $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{R}^7$  and  $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{NR}^5\text{R}^{10}$ ;

$m$  is 0 to 4, and

$n$  is 1 to 4.

The compounds of Formula III can be useful as protein kinase inhibitors  
15 and can be useful in the treatment and prevention of proliferative diseases, for example, cancer, inflammation and arthritis. They may also be useful in the treatment of neurodegenerative diseases such Alzheimer's disease, cardiovascular diseases, viral diseases and fungal diseases.

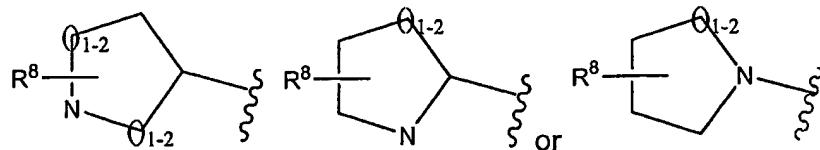
20

### Detailed Description

In one embodiment, the present invention discloses pyrazolo[1,5-a]pyrimidine compounds which are represented by structural Formula III, or a pharmaceutically acceptable salt or solvate thereof, wherein the various moieties are as described above.

25 In another embodiment,  $\text{R}^2$  is halogen,  $\text{CF}_3$ ,  $\text{CN}$ , lower alkyl,  $-\text{OR}^6$ , cycloalkyl,  $-\text{C}(\text{O})\text{OR}^6$ ,  $-\text{CH}_2\text{OR}^6$ , aryl or heteroaryl.

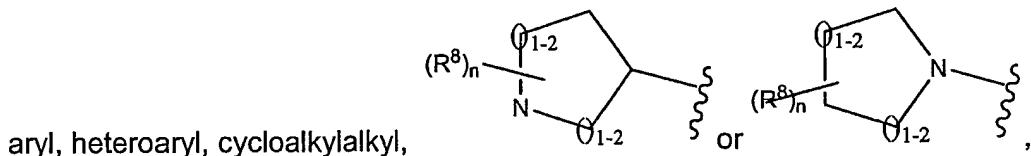
In another embodiment,  $\text{R}^3$  is H, halogen, lower alkyl, aryl, heteroaryl,  $\text{C}(\text{O})\text{OR}^4$ , cycloalkyl,  $-\text{NR}^5\text{R}^6$ , heterocyclalkyl, cycloalkylalkyl,



wherein each of said alkyl, aryl, heteroaryl, heterocycl and cycloalkyl are unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen,  $\text{CF}_3$ ,  $\text{OCF}_3$ , lower alkyl,  $\text{CN}$  and  $\text{OR}^5$ .

5 In another embodiment,  $\text{R}^4$  is H or lower alkyl.  
 In another embodiment,  $\text{R}^5$  is H or lower alkyl.  
 In another embodiment,  $m$  is 0 to 2.  
 In an additional embodiment,  $\text{R}^2$  is halogen,  $\text{CF}_3$ ,  $\text{CN}$ , cyclopropyl, lower alkyl, aryl,  $\text{CH}_2\text{OR}^6$ ,  $\text{C}(\text{O})\text{OR}^6$ , or  $-\text{OR}^6$ .

10 In an additional embodiment,  $\text{R}^3$  is H, lower alkyl, cycloalkyl,  $\text{C}(\text{O})\text{OR}^4$ ,

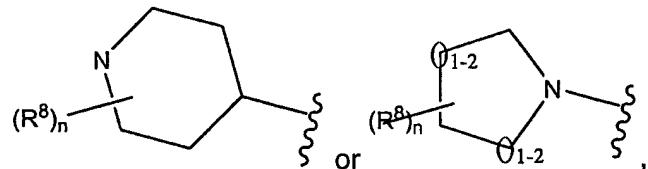


aryl, heteroaryl, cycloalkylalkyl,

wherein each of said alkyl, cycloalkyl, heteroaryl and aryl are unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group

15 consisting of halogen,  $\text{CF}_3$ , lower alkyl,  $\text{OMe}$  and  $\text{CN}$ .

In an additional embodiment,  $\text{R}^3$  is



In an additional embodiment,  $\text{R}^4$  is H.

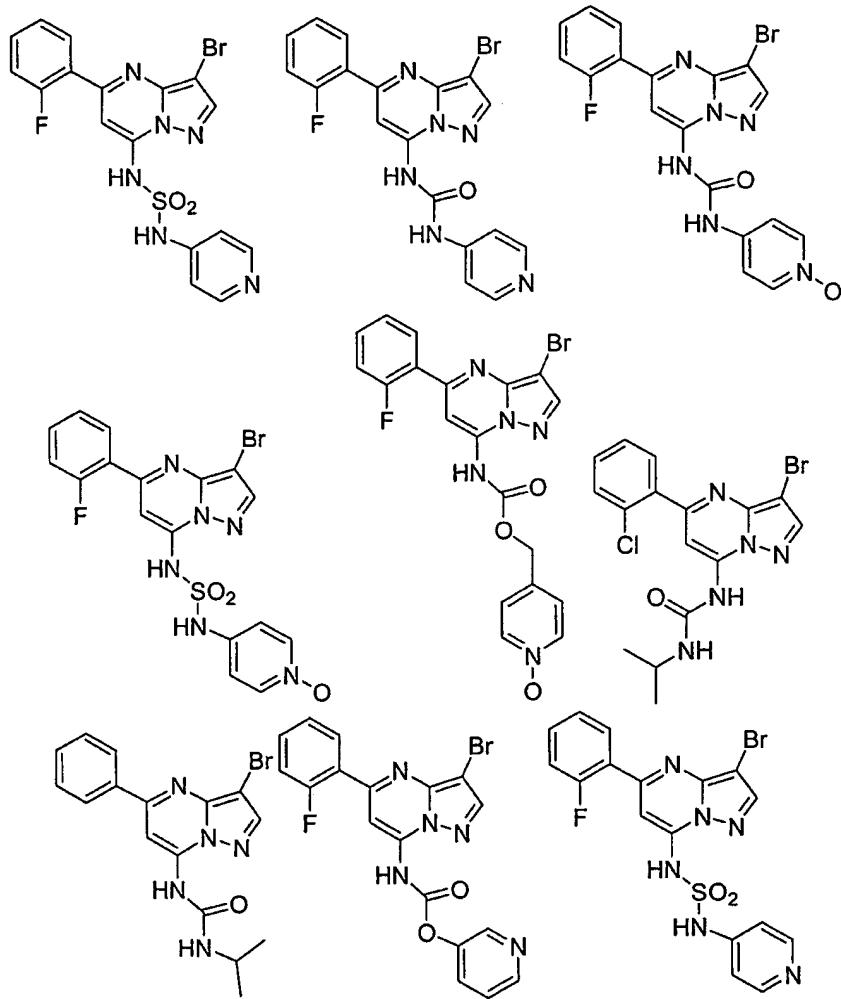
In an additional embodiment,  $\text{R}^5$  is H.

20 In an additional embodiment,  $\text{R}^8$  is  $-\text{CH}_2\text{OH}$  or  $-\text{CH}_2\text{OCH}_3$ .

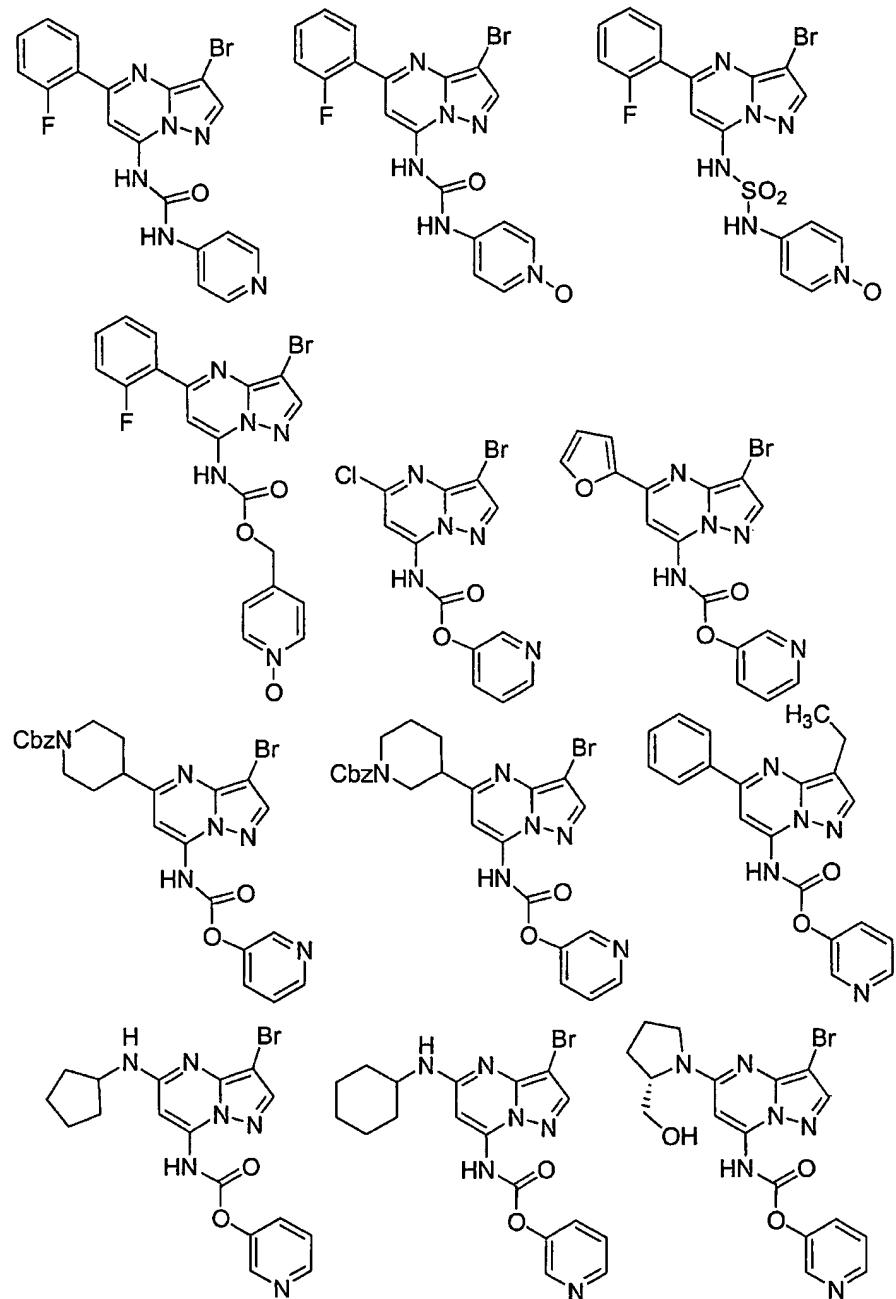
In an additional embodiment,  $m$  is 0.

In an additional embodiment,  $n$  is 1 or 2.

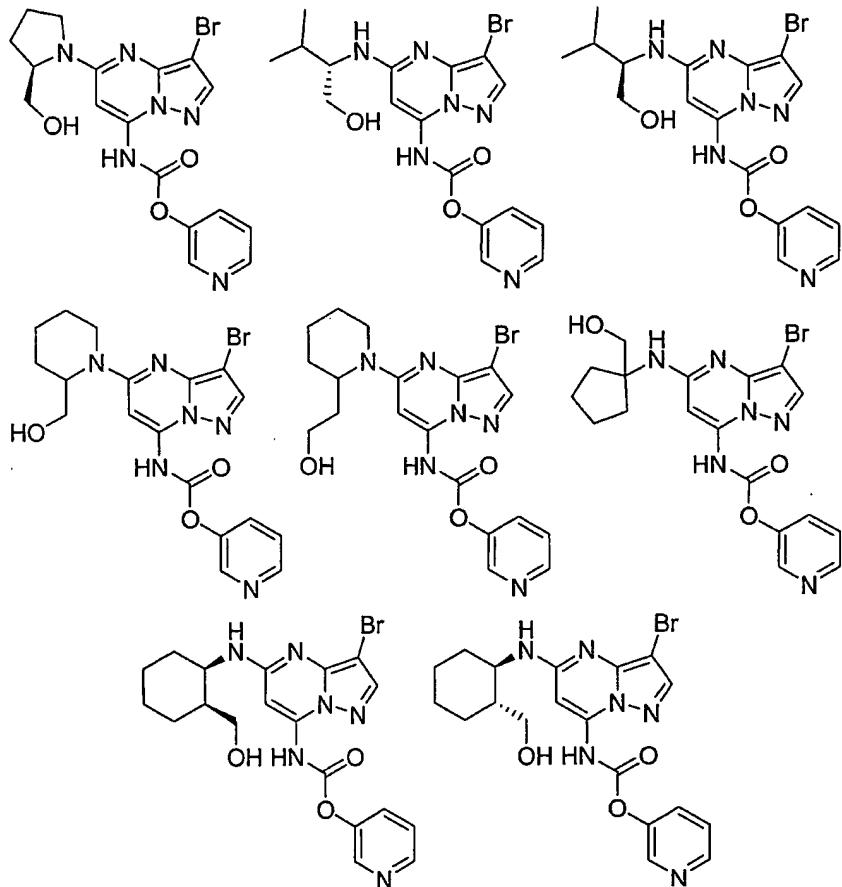
An inventive group of compounds are shown in **Table 1**.

Table 1

9



10



As used above, and throughout this disclosure, the following terms,

5 unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain.

10 Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain.

More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or

15 branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different,

each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)<sub>2</sub>, carboxy and -C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

5 "Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more

10 lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by

15 one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur

atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, 5 triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

10 "Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

15 "Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

20 "Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, 25 cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

30 "Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on

the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl,

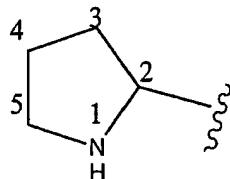
5 aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl,  $Y_1Y_2N$ -,  $Y_1Y_2N$ -alkyl-,  $Y_1Y_2NC(O)$ - and  $Y_1Y_2NSO_2$ -, wherein  $Y_1$  and  $Y_2$  may be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl.

10 "Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the 15 ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any -NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protected moieties are also considered 20 part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, 25 piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, and the like.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom.

30 Thus, for example, in the ring:

14



there is no -OH attached directly to carbons marked 2 and 5.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

5 "Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

10 "Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

15 "Alkoxy carbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxy carbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxy carbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxy carbonyl groups include phenoxy carbonyl and naphthoxy carbonyl. The bond to the parent moiety is through the carbonyl.

20 "Aralkoxy carbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxy carbonyl group is benzyloxy carbonyl. The bond to the parent moiety is through the carbonyl.

25 "Alkylsulfonyl" means an alkyl-S(O<sub>2</sub>)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O<sub>2</sub>)- group. The bond to the parent moiety is through the sulfonyl.

30 The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an

5 efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the

10 hydrogen atom to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by

15 reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R<sup>2</sup>, etc.) occurs more than one time in any constituent or in Formula III, its definition on each occurrence is independent of its definition at every other occurrence.

20 As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

25 Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula III or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American

Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like.

10 "Hydrate" is a solvate wherein the solvent molecule is  $H_2O$ .

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the CDK(s) and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

15 The compounds of Formula III can form salts which are also within the scope of this invention. Reference to a compound of Formula III herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic 20 bases. In addition, when a compound of Formula III contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein.

Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are 25 preferred, although other salts are also useful. Salts of the compounds of the Formula III may be formed, for example, by reacting a compound of Formula III with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

30 Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates,

camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like.

5     Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic

10    Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

25    All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula III, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

30    All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and

prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

15 The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula III can be inhibitors of protein kinases such as the cyclin dependent kinases (CDKs), for example, CDC2 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK7 and CDK8. The novel compounds of Formula III are expected to be useful in the therapy of proliferative diseases such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative (e.g., ocular retinopathy), neuronal, alopecia and cardiovascular disease. Many of these diseases and disorders are listed in U.S. 6,413,974 cited earlier, the disclosure of which is incorporated herein.

20 More specifically, the compounds of Formula III can be useful in the treatment of a variety of cancers, including (but not limited to) the following: carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T- cell lymphoma,

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Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome, romyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and

5 rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

10 Due to the key role of CDKs in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, 15 glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

20 Compounds of Formula III may also be useful in the treatment of Alzheimer's disease, as suggested by the recent finding that CDK5 is involved in the phosphorylation of tau protein (*J. Biochem.*, (1995) 117, 741-749).

Compounds of Formula III may induce or inhibit apoptosis. The apoptotic response is aberrant in a variety of human diseases. Compounds of Formula III, as modulators of apoptosis, will be useful in the treatment of cancer (including but not limited to those types mentioned hereinabove), viral infections (including 25 but not limited to herpesvirus, poxvirus, Epstein- Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), 30 neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis,

retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including 5 but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

Compounds of Formula III, as inhibitors of the CDKs, can modulate the 10 level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

Compounds of Formula III may also be useful in the chemoprevention of 15 cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

Compounds of Formula III may also be useful in inhibiting tumor 20 angiogenesis and metastasis.

Compounds of Formula III may also act as inhibitors of other protein kinases, e.g., protein kinase C, her2, raf 1, MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF receptor, PI3 kinase, wee1 kinase, Src, Abl and thus be effective in the treatment of diseases associated with other protein kinases.

25 Another aspect of this invention is a method of treating a mammal (e.g., human) having a disease or condition associated with the CDKs by administering a therapeutically effective amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound to the mammal.

30 A preferred dosage is about 0.001 to 500 mg/kg of body weight/day of the compound of Formula III. An especially preferred dosage is about 0.01 to 25

mg/kg of body weight/day of a compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound.

The compounds of this invention may also be useful in combination (administered together or sequentially) with one or more of anti-cancer

5 treatments such as radiation therapy, and/or one or more anti-cancer agents selected from the group consisting of cytostatic agents, cytotoxic agents (such as for example, but not limited to, DNA interactive agents (such as cisplatin or doxorubicin)); taxanes (e.g. taxotere, taxol); topoisomerase II inhibitors (such as etoposide); topoisomerase I inhibitors (such as irinotecan (or CPT-11),  
10 camptostar, or topotecan); tubulin interacting agents (such as paclitaxel, docetaxel or the epothilones); hormonal agents (such as tamoxifen); thymidilate synthase inhibitors (such as 5-fluorouracil); anti-metabolites (such as methotrexate); alkylating agents (such as temozolomide (TEMODAR<sup>TM</sup> from Schering-Plough Corporation, Kenilworth, New Jersey), cyclophosphamide);  
15 Farnesyl protein transferase inhibitors (such as, SARASAR<sup>TM</sup>(4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide, or SCH 66336 from Schering-Plough Corporation, Kenilworth, New Jersey), tipifarnib (Zarnestra<sup>®</sup> or R115777 from Janssen Pharmaceuticals), L778,123 (a farnesyl protein  
20 transferase inhibitor from Merck & Company, Whitehouse Station, New Jersey), BMS 214662 (a farnesyl protein transferase inhibitor from Bristol-Myers Squibb Pharmaceuticals, Princeton, New Jersey); signal transduction inhibitors (such as, Iressa (from Astra Zeneca Pharmaceuticals, England), Tarceva (EGFR kinase inhibitors), antibodies to EGFR (e.g., C225), GLEEVEC<sup>TM</sup> (C-abl kinase inhibitor  
25 from Novartis Pharmaceuticals, East Hanover, New Jersey); interferons such as, for example, intron (from Schering-Plough Corporation), Peg-Intron (from Schering-Plough Corporation); hormonal therapy combinations; aromatase combinations; ara-C, adriamycin, cytoxan, and gemcitabine.

Other anti-cancer (also known as anti-neoplastic) agents include but are  
30 not limited to Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine,

Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, oxaliplatin (ELOXATIN™ from Sanofi-Synthelabo Pharmaceuticals, France), Pentostatine, Vinblastine,

5 Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17 $\alpha$ -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone,

10 Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or

15 Hexamethylmelamine.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range. For example, the CDC2 inhibitor olomucine has been found to act synergistically with known cytotoxic agents in inducing apoptosis (*J. Cell Sci.*, (1995) 108, 2897. Compounds of Formula III may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of Formula III may be administered either prior to or after administration of the known anticancer or cytotoxic agent. For example, the cytotoxic activity of the cyclin-dependent kinase inhibitor flavopiridol is affected by the sequence of administration with anticancer agents. *Cancer Research*, (1997) 57, 3375. Such techniques are within the skills of persons skilled in the art as well as attending physicians.

30 Accordingly, in an aspect, this invention includes combinations comprising an amount of at least one compound of Formula III, or a pharmaceutically

acceptable salt or solvate thereof, and an amount of one or more anti-cancer treatments and anti-cancer agents listed above wherein the amounts of the compounds/ treatments result in desired therapeutic effect.

The pharmacological properties of the compounds of this invention may 5 be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which are described later have been carried out with the compounds according to the invention and their salts.

This invention is also directed to pharmaceutical compositions which comprise at least one compound of Formula III, or a pharmaceutically acceptable 10 salt or solvate of said compound and at least one pharmaceutically acceptable carrier.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, 15 dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. 20 Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 18<sup>th</sup> Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. 25 As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and 30 solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

5 The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of this invention may also be delivered subcutaneously.

10 Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

15 The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the 20 requirements of the patient and the severity of the condition being treated.

Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

25 The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 30 mg/day, in two to four divided doses.

Another aspect of this invention is a kit comprising a therapeutically effective amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

5 Yet another aspect of this invention is a kit comprising an amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and an amount of at least one anticancer therapy and/or anti-cancer agent listed above, wherein the amounts of the two or more ingredients result in desired therapeutic effect.

10 The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

Where NMR data are presented,  $^1\text{H}$  spectra were obtained on either a  
15 Varian VXR-200 (200 MHz,  $^1\text{H}$ ), Varian Gemini-300 (300 MHz) or XL-400 (400 MHz) and are reported as ppm down field from Me<sub>4</sub>Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column:  
20 Altech platinum C18, 3 micron, 33mm x 7mm ID; gradient flow: 0 min – 10% CH<sub>3</sub>CN, 5 min – 95% CH<sub>3</sub>CN, 7 min – 95% CH<sub>3</sub>CN, 7.5 min – 10% CH<sub>3</sub>CN, 9 min – stop. The retention time and observed parent ion are given.

The following solvents and reagents may be referred to by their abbreviations in parenthesis:

25 Thin layer chromatography: TLC  
dichloromethane: CH<sub>2</sub>Cl<sub>2</sub>  
ethyl acetate: AcOEt or EtOAc  
methanol: MeOH  
trifluoroacetate: TFA  
30 triethylamine: Et<sub>3</sub>N or TEA  
butoxycarbonyl: n-Boc or Boc

nuclear magnetic resonance spectroscopy: NMR

liquid chromatography mass spectrometry: LCMS

high resolution mass spectrometry: HRMS

milliliters: mL

5 millimoles: mmol

microliters:  $\mu$ l

grams: g

milligrams: mg

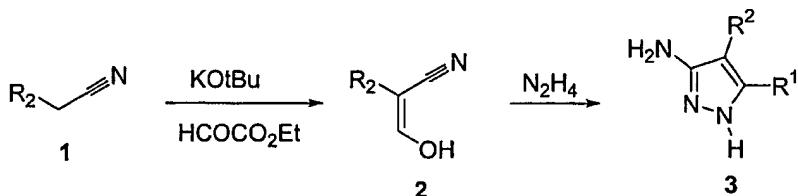
room temperature or rt (ambient): about 25°C.

10

### EXAMPLES

In general, the compounds described in this invention can be prepared through the general routes described below in Scheme 1. Treatment of the

Scheme 1

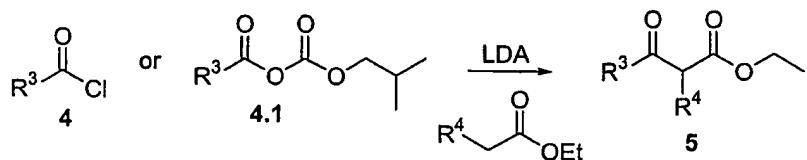


15

starting nitrile with potassium t-butoxide and ethyl formate gives rise to the intermediate enol 2 which upon treatment with hydrazine gives the desired substituted 3-aminopyrazole. Condensation of compounds of type 3 with the appropriately functionalized keto ester of type 5 gives rise to the pyridones 6 as shown in Scheme 3. The keto esters used in this general route are either commercially available or can be made as illustrated in Scheme 2.

20

Scheme 2



25

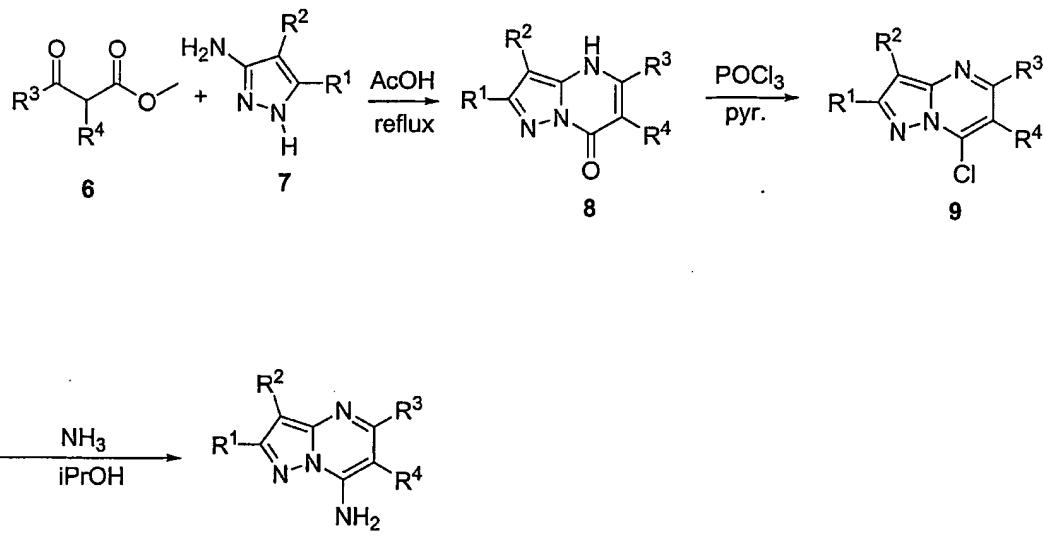
The chlorides of type 9 can be prepared by treatment of the pyridones 8

with  $\text{POCl}_3$ . When  $\text{R}^2$  is equal to H, substitution in this position is possible on the

compounds of type 9 by electrophilic halogenation, acylation, and various other electrophilic aromatic substitutions.

Introduction of the N7-amino functionality can be accomplished through displacement of the chloride of compounds of type 9 by reaction with ammonia in 5 2-propanol as shown in Scheme 3.

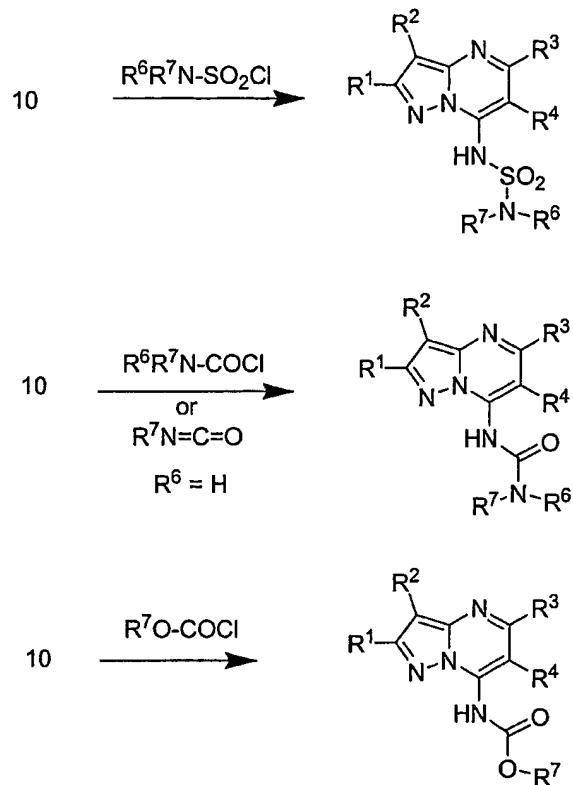
Scheme 3



The C-7 amino intermediate 10 is then acylated or sulfonylated with the appropriate sulfamoyl chloride, carbamoyl chloride or chloroformate to give the 10 desired products as shown in Scheme 4.

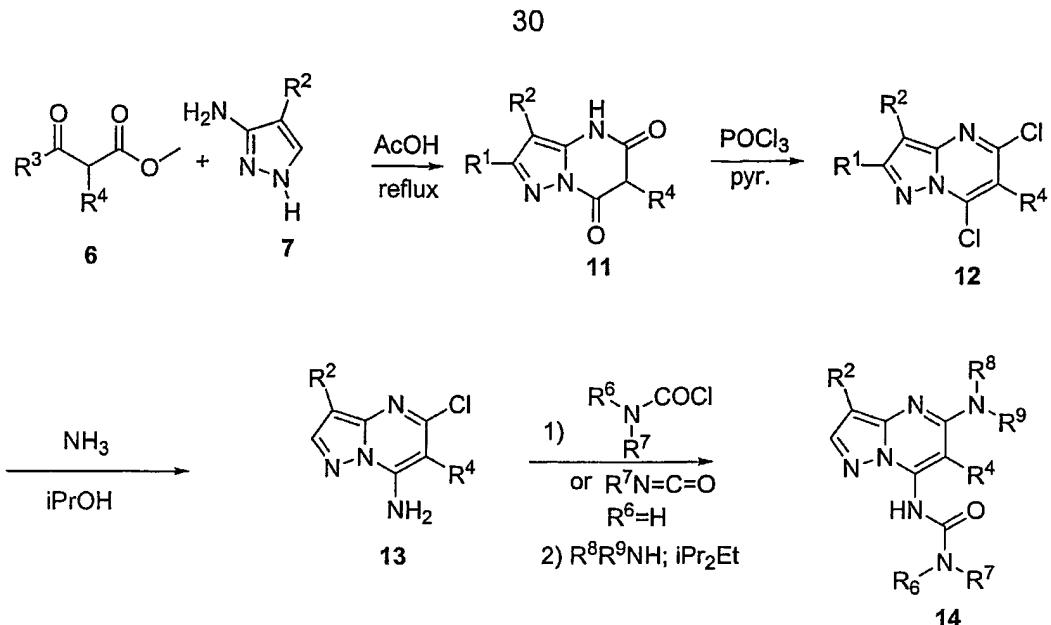
Scheme 4

29



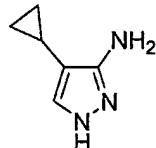
When  $R^3 = OEt$  in compounds of type 6, the dichlorides of type 12 can easily be prepared as outlined in Scheme 4. Selective displacements of the 7-chloride gives rise to compounds of type 13, which can readily be converted to products of type 14 or the corresponding sulfonimides.

**SCHEME 5**

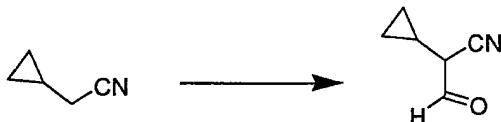


### Preparative Examples:

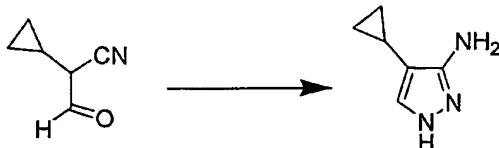
### PREPARATIVE EXAMPLE 1:



## 5 Step A:



A procedure in German patent DE 19834047 A1, p 19 was followed. To a solution of KOtBu (6.17 g, 0.055 mol) in anhydrous THF (40 mL) was added, dropwise, a solution of cyclopropylacetonitrile (2.0 g, 0.025 mol) and ethyl formate (4.07 g, 0.055 mol) in anhydrous THF (4 mL). A precipitate formed immediately. This mixture was stirred for 12 hr. It was concentrated under vacuum and the residue stirred with Et<sub>2</sub>O (50 mL). The resulting residue was decanted and washed with Et<sub>2</sub>O (2 x 50 mL) and Et<sub>2</sub>O removed from the residue under vacuum. The residue was dissolved in cold H<sub>2</sub>O (20 mL) and pH adjusted to 4 – 5 with 12 N HCl. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 50 mL). The organic layers were combined, dried over MgSO<sub>4</sub> and concentrated under vacuum to give the aldehyde as a tan liquid.

Step B:

The product from Preparative Example 1, Step A (2.12 g, 0.0195 mol), NH<sub>2</sub>NH<sub>2</sub> · H<sub>2</sub>O (1.95 g, 0.039 mol) and 1.8 g (0.029 mole) of glacial CH<sub>3</sub>CO<sub>2</sub>H 5 (1.8 g, 0.029 mol) were dissolved in EtOH (10 mL). It was refluxed for 6 hr and concentrated under vacuum. The residue was slurried in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) and the pH adjusted to 9 with 1N NaOH. The organic layer was washed with brine, dried over MgSO<sub>4</sub> and concentrated under vacuum to give the product as a waxy orange solid.

10 PREPARATIVE EXAMPLES 2-4:

By essentially the same procedure set forth in Preparative Example 1, only substituting the nitrile shown in Column 2 of Table 2, the compounds in Column 3 of Table 2 were prepared:

TABLE 2

15

Prep. Ex.	Column 2	Column 3
2		
3		

PREPARATIVE EXAMPLE 4:

The reactions were done as outlined in (K. O. Olsen, *J. Org. Chem.*,

(1987) 52, 4531 – 4536). Thus, to a stirred solution of lithium diisopropylamide in THF at -65 to -70 °C was added freshly distilled ethyl acetate, dropwise. The resulting solution was stirred for 30 min and the acid chloride was added as a solution in THF. The reaction mixture was stirred at -65 to -70 °C for 30 min 5 and then terminated by the addition of 1 N HCl solution. The resulting two-phased mixture was allowed to warm to ambient temperature. The resulting mixture was diluted with EtOAc (100 mL) the organic layer was collected. The aqueous layer was extracted with EtOAc (100 mL). The organic layers were combined, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo* to give 10 the crude  $\beta$ -keto esters, which were used in the subsequent condensations.

PREPARATIVE EXAMPLES 5-10:

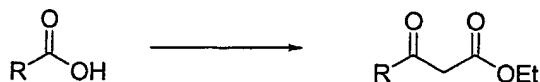
By essentially the same procedure set forth in Preparative Example 4 only substituting the acid chlorides shown in Column 2 of Table 3, the  $\beta$ -keto esters shown in Column 3 of Table 3 were prepared:

15

TABLE 3

Prep. Ex.	Column 2	Column 3	DATA
5			Yield = 99% LCMS: M <sup>+</sup> = 223
6			Yield = 99% LCMS: M <sup>+</sup> = 253
7			Yield = 80% LCMS: M <sup>+</sup> = 261
8			Yield = 93% M <sup>+</sup> = 199

9			Yield=93%
10			Yield=100%

PREPARATIVE EXAMPLE 11:

5 To a solution of the acid in THF was added  $\text{Et}_3\text{N}$ , followed by isobutyl chloroformate at  $-20$  to  $-30$  °C. After the mixture was stirred for 30 min at  $-20$  to  $-30$  °C, triethylamine hydrochloride was filtered off under argon, and the filtrate was added to the LDA-EtOAc reaction mixture (prepared as outlined in Method A) at  $-65$  to  $-70$  °C. After addition of 1 N HCl, followed by routine workup of the

10 reaction mixture and evaporation of the solvents, the crude  $\beta$ -keto esters were isolated. The crude material was used in the subsequent condensations.

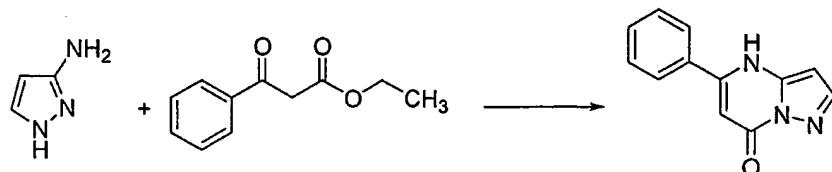
PREPARATIVE EXAMPLES 12-13.12:

By essentially the same conditions set forth in Preparative Example 11 only substituting the carboxylic acid shown in Column 2 of Table 4, the

15 compounds shown in Column 3 of Table 4 were prepared:

TABLE 4

Prep. Ex.	<u>Column 2</u>	<u>Column 3</u>	<u>DATA</u>
12			Yield = 99% MH <sup>+</sup> = 213
13			Yield = 70% MH <sup>+</sup> = 275
13.10			Yield = 99 MH <sup>+</sup> = 199
13.11			Yield = 99 MH <sup>+</sup> = 334
13.12			Yield = 99 MH <sup>+</sup> = 334

5 PREPARATIVE EXAMPLE 14:

A solution of 3-aminopyrazole (2.0g, 24.07 mmol) and ethyl benzoylacetate (4.58 mL, 1.1 eq.) in AcOH (15 mL) was heated at reflux for 3 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting solid was diluted with EtOAc and filtered to give a white solid (2.04 g, 40% yield).

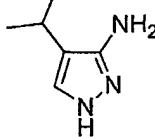
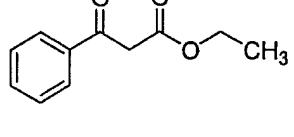
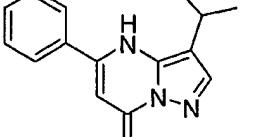
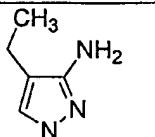
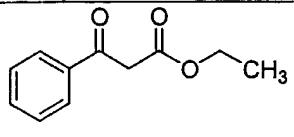
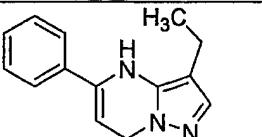
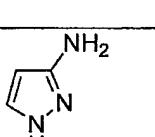
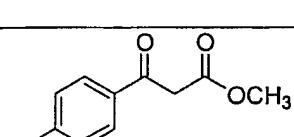
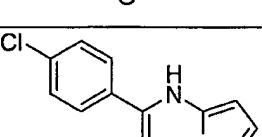
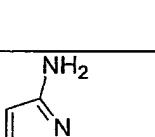
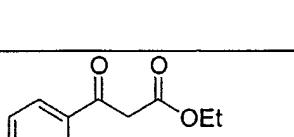
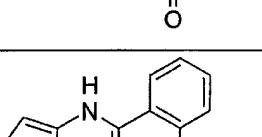
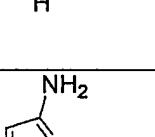
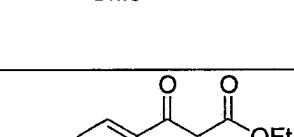
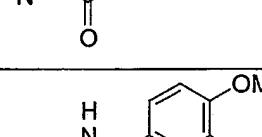
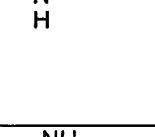
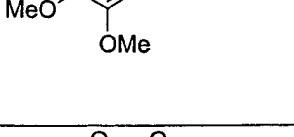
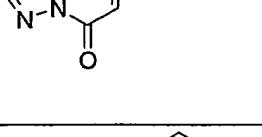
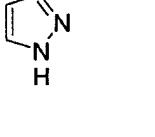
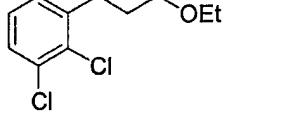
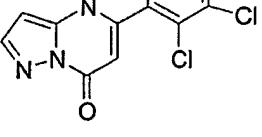
PREPARATIVE EXAMPLES 15-32.15:

By essentially the same procedure set forth in Preparative Example 14 only substituting the aminopyrazole shown in Column 2 of Table 5 and the ester

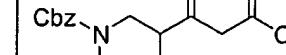
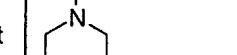
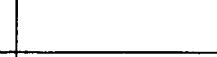
shown in Column 3 of Table 5, the compounds shown in Column 4 of Table 5 were prepared:

TABLE 5

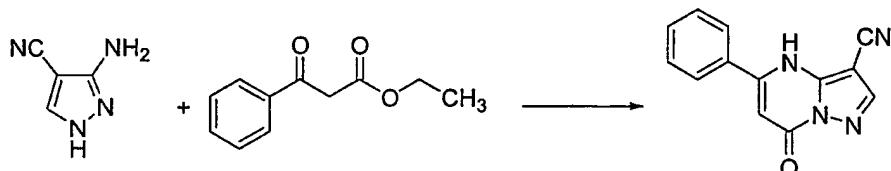
Prep. Ex.	<u>Column 2</u>	<u>Column 3</u>	<u>Column 4</u>
15			
16			
17			
18			
19			
20			

21			
22			
23			
24			
25			
26			
27			

28			
29			
30			
31			
32			
32.11			
32.12			
32.13			

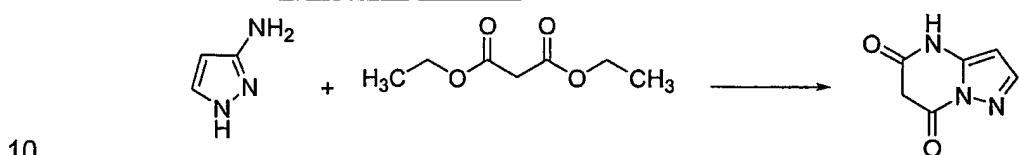
32.14			
32.15			

### PREPARATIVE EXAMPLE 33:



Ethyl benzoylacetate (1.76 mL, 1.1 eq.) and 3-amino-4-cyanopyrazole (1.0 g, 9.25 mmol) in AcOH (5.0 mL) and H<sub>2</sub>O (10 mL) was heated at reflux 72 hours. The resulting solution was cooled to room temperature, concentrated *in vacuo*, and diluted with EtOAc. The resulting precipitate was filtered, washed with EtOAc, and dried *in vacuo* (0.47 g, 21% yield).

### PREPARATIVE EXAMPLE 33.10:



A procedure in US patent 3,907,799 was followed. Sodium (2.3 g, 2 eq.) was added to EtOH (150 mL) portionwise. When the sodium was completely dissolved, 3-aminopyrazole (4.2 g, 0.05 mol) and diethyl malonate (8.7 g, 1.1 eq.) were added and the resulting solution heated to reflux for 3 hours. The resulting suspension was cooled to room temperature and filtered. The filter cake was washed with EtOH (100 mL) and dissolved in water (250 mL). The resulting solution was cooled in an ice bath and the pH adjusted to 1-2 with

concentrated HCl. The resulting suspension was filtered, washed with water (100 mL) and dried under vacuum to give a white solid (4.75 g, 63% yield).

PREPARATIVE EXAMPLES 33.11-33.12:

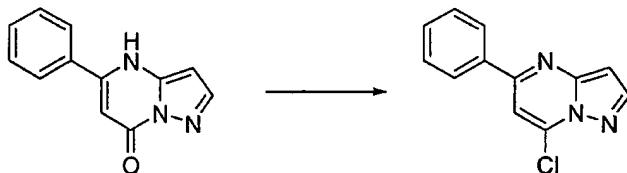
By essentially the same procedure set forth in Preparative Example 33.10  
 5 only substituting the compound shown in Column 2 of Table 5.1, the compounds shown in Column 3 of Table 5.1 are prepared:

TABLE 5.1

Prep. Ex.	<u>Column 2</u>	<u>Column 3</u>
33.11		
33.12		

PREPARATIVE EXAMPLE 34:

10



A solution of the compound prepared in Preparative Example 14 (1.0 g, 4.73 mmol) in  $\text{POCl}_3$  (5 mL) and pyridine (0.25 mL) was stirred at room temperature 3 days. The resulting slurry was diluted with  $\text{Et}_2\text{O}$ , filtered, and the solid residue washed with  $\text{Et}_2\text{O}$ . The combined  $\text{Et}_2\text{O}$  washings were cooled to 15  $0^\circ\text{C}$  and treated with ice. When the vigorous reaction ceased, the resulting mixture was diluted with  $\text{H}_2\text{O}$ , separated, and the aqueous layer extracted with  $\text{Et}_2\text{O}$ . The combined organics were washed with  $\text{H}_2\text{O}$  and saturated  $\text{NaCl}$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give a pale yellow solid (0.86 g, 79% yield). LCMS:  $\text{MH}^+=230$ .

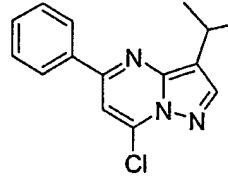
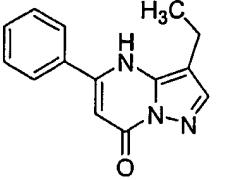
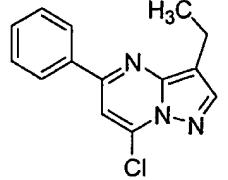
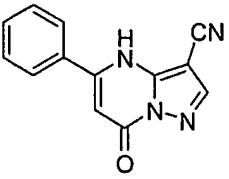
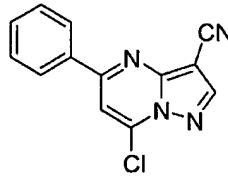
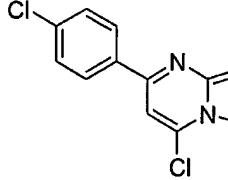
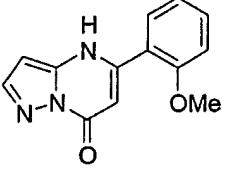
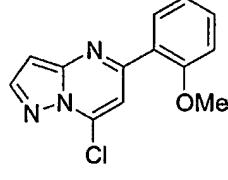
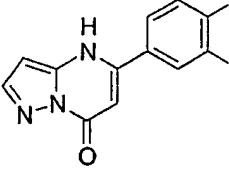
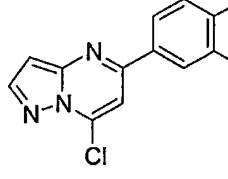
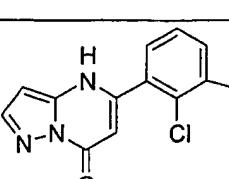
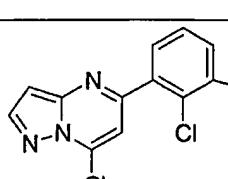
PREPARATIVE EXAMPLE 35-53.15:

By essentially the same procedure set forth in Preparative Example 34, only substituting the compound shown in Column 2 of Table 6, the compounds shown in Column 3 of Table 6 were prepared:

5

TABLE 6

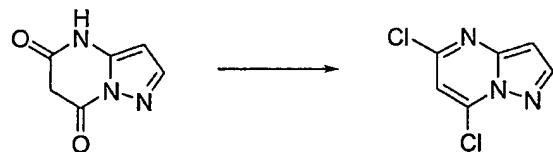
Prep. Ex.	<u>Column 2</u>	<u>Column 3</u>	<u>DATA</u>
35			LCMS: $MH^+ = 248$
36			
37			LCMS: $MH^+ = 298$
38			LCMS: $MH^+ = 196$
39			LCMS: $MH^+ = 210$
40			

41			LCMS: $MH^+ = 272$
42			
43			LCMS: $MH^+ = 255$
44			
45			Yield = 65% LCMS: $MH^+ = 260$
46			Yield = 35% LCMS: $MH^+ = 290$
47			Yield = 32% LCMS: $MH^+ = 298$

48			Yield = 45% LCMS: $MH^+ = 236$
49			Yield = 100% LCMS: $MH^+ = 250$
50			Yield = 88% LCMS: $MH^+ = 314$
51			Yield = 43% LCMS: $MH^+ = 223$
52			Yield = 30% LCMS: $MH^+ = 295$
53			Yield = 98% LCMS: $MH^+ = 244$
53.11			
53.12			

53.13			Yield = 96 $MH^+ = 371$
53.14			Yield = 99 $MH^+ = 371$
53.15			Yield = quant. $MH^+ = 236$

PREPARATIVE EXAMPLE 53.16



5  $POCl_3$  (62 mL) was cooled to 5 °C under nitrogen and dimethylaniline (11.4 g, 2.8 eq.) and the compound prepared in Preparative Example 33.10 (4.75 g, 0.032 mol). The reaction mixture was warmed to 60 °C and stirred overnight. The reaction mixture was cooled to 30 °C and the  $POCl_3$  was distilled off under reduced pressure. The residue was dissolved in  $CH_2Cl_2$  (300 mL) and poured onto ice. After stirring 15 minutes, the pH of the mixture was adjusted to 7-8 with solid  $NaHCO_3$ . The layers were separated and the organic layer was washed with  $H_2O$  (3 x 200 mL), dried over  $MgSO_4$ , filtered, and concentrated. The crude product was purified by flash chromatography using a 50 : 50  $CH_2Cl_2$  : hexanes solution as eluent to elute the dimethyl aniline. The eluent was then 10 changed to 75 : 25  $CH_2Cl_2$  : hexanes to elute the desired product (4.58 g, 77% yield). MS:  $MH^+ = 188$ .

15

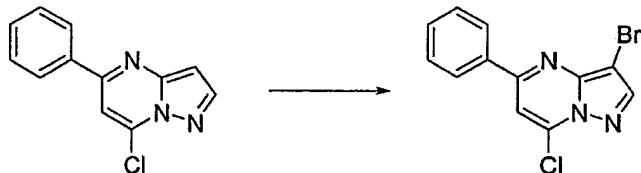
PREPARATIVE EXAMPLES 53.17-53.18

By essentially the same procedure set forth in Preparative Example 53.16 only substituting the compound in Column 2 of Table 6.10, the compounds shown in Column 3 of Table 6.10 are prepared:

5

TABLE 6.10

Prep. Ex.	<u>Column 2</u>	<u>Column 3</u>
53.17		
53.18		

PREPARATIVE EXAMPLE 54:

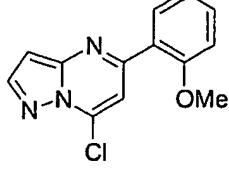
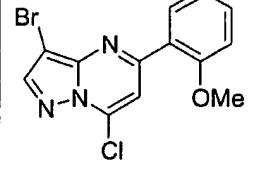
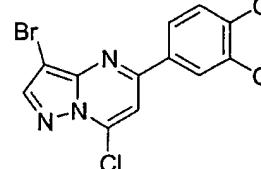
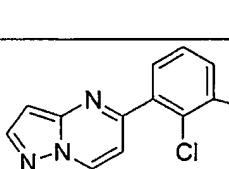
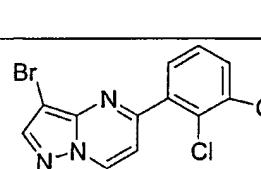
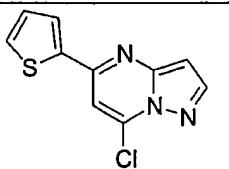
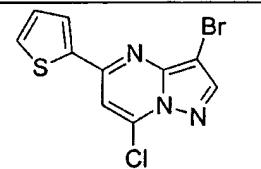
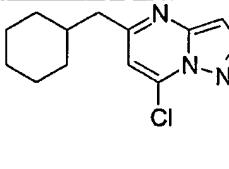
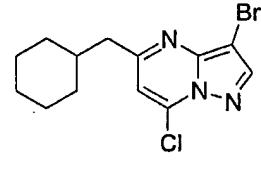
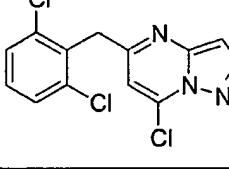
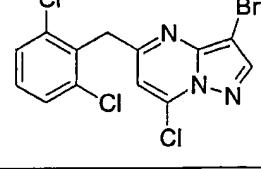
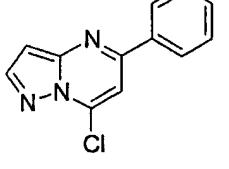
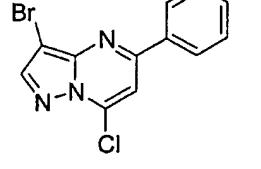
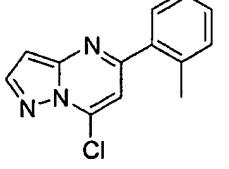
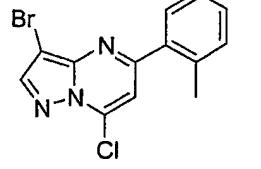
10 A solution of the compound prepared in Preparative Example 34 (0.10 g, 0.435 mmol) in CH<sub>3</sub>CN (3 mL) was treated with NBS (0.085 g, 1.1 eq.). The reaction mixture was stirred at room temperature 1 hour and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 20% EtOAc-in-hexanes solution as eluent (0.13 g, 100% yield). LCMS: 15 MH<sup>+</sup>=308.

PREPARATIVE EXAMPLES 55-68.15:

By essentially the same procedure set forth in Preparative Example 54 only substituting the compounds shown in Column 2 of Table 7, the compounds shown in Column 3 of Table 7 were prepared:

TABLE 7

Prep. Ex.	<u>Column 2</u>	<u>Column 3</u>	<u>DATA</u>
55			LCMS: $MH^+ = 326$
56			LCMS: $MH^+ = 342$
57			LCMS: $MH^+ = 376$
58			LCMS: $MH^+ = 274$
59			LCMS: $MH^+ = 288$
60			

61			Yield = 75% LCMS: $MH^+ = 338$
62			Yield = 52% LCMS: $MH^+ = 368$
63			Yield = 87% LCMS: $MH^+ = 376$
64			Yield = 100% LCMS: $MH^+ = 316$
65			Yield = 92% LCMS: $MH^+ = 330$
66			Yield = 82% LCMS: $MH^+ = 395$
67			Yield = 88% LCMS: $MH^+ = 308$
68			Yield = 100% LCMS: $MH^+ = 322$

68.10			
68.11			
68.12			Yield = 99 $MH^+ = 449$
68.13			Yield = 95 $MH^+ = 449$
68.14			$MH^+ = 266$
68.15			Yield = quant. $MH^+ = 314$

PREPARATIVE EXAMPLE 69:



A solution of the compound prepared in Preparative Example 35 (0.3 g, 5 1.2 mmol) in  $CH_3CN$  (15 mL) was treated with NCS (0.18 g, 1.1 eq.) and the resulting solution heated to reflux 4 hours. Additional NCS (0.032 g, 0.2 eq.) added and the resulting solution was stirred at reflux overnight. The reaction

mixture was cooled to room temperature, concentrated *in vacuo* and the residue purified by flash chromatography using a 20% EtOAc in hexanes solution as eluent (0.28 g, 83% yield). LCMS:  $MH^+ = 282$ .

PREPARATIVE EXAMPLE 70:

5 By essentially the same procedure set forth in Preparative Example 69 only substituting the compound shown in Column 2 of Table 8, the compound shown in Column 3 of Table 8 was prepared:

TABLE 8

<u>Prep. Ex.</u>	<u>Column 2</u>	<u>Column 3</u>	<u>DATA</u>
70			Yield = 82% LCMS: $MH^+ = 286$

10

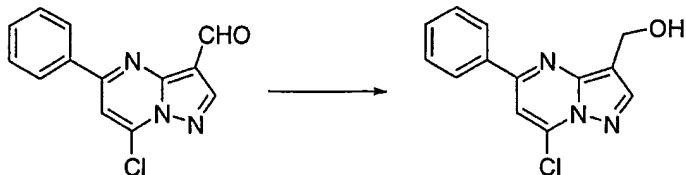
PREPARATIVE EXAMPLE 71:



15 To a solution of the compound from Preparative Example 34 (1.0 g, 4.35 mmol) in DMF (6 mL) was added  $POCl_3$  (1.24 mL, 3.05 eq.) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was cooled to 0°C and the excess  $POCl_3$  was quenched by the addition of ice. The resulting solution was neutralized with 1N NaOH, diluted with  $H_2O$ , and extracted with  $CH_2Cl_2$ . The combined organics were dried over  $Na_2SO_4$ , filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography using a 5% MeOH in  $CH_2Cl_2$  solution as eluent (0.95 g, 85% yield). LCMS:  $MH^+ = 258$ .

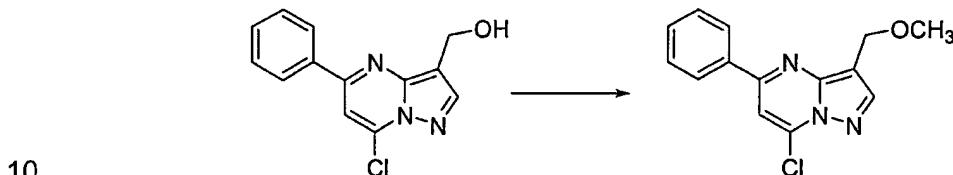
PREPARATIVE EXAMPLE 72:

49



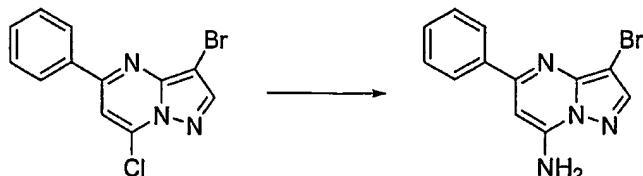
To a solution of the product of Preparative Example 71 (0.25 g, 0.97 mmol) in THF was added NaBH<sub>4</sub> (0.041 g, 1.1 eq.) and the resulting solution was stirred at room temperature overnight. The reaction mixture was quenched 5 by the addition of H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 60: 40 hexanes : EtOAc mix as eluent (0.17 g, 69% yield). LCMS: MH<sup>+</sup>=260.

PREPARATIVE EXAMPLE 73:



A solution of the compound prepared in Preparative Example 72 (0.12 g, 0.462 mmol), dimethyl sulfate (0.088 mL, 2.0 eq), 50% NaOH (0.26 mL) and catalytic Bu<sub>4</sub>NBr in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was stirred at room temperature overnight. The reaction mixture was diluted with H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The 15 combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 30% EtOAc-in-hexanes solution as eluent (0.062 g, 48% yield).

PREPARATIVE EXAMPLE 74:



The compound prepared in Preparative Example 54 (3.08 g, 10.0 mmol), 2.0 M NH<sub>3</sub> in 2-propanol (50 mL, 100.0 mmol), and 37 % aqueous NH<sub>3</sub> (10.0 mL) were stirred in a closed pressure vessel at 50°C for 1 day. The solvent was evaporated and the crude product was purified by flash chromatography using 20

3:1 CH<sub>2</sub>Cl<sub>2</sub>:EtOAc as eluent. Pale yellow solid (2.30 g, 80%) was obtained.

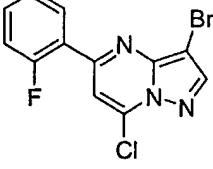
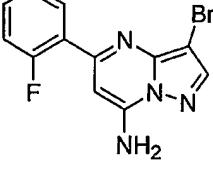
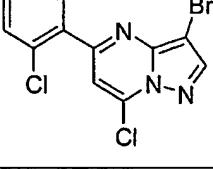
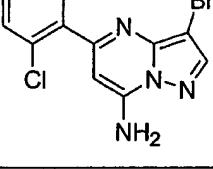
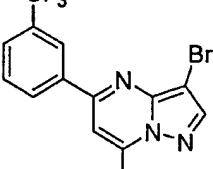
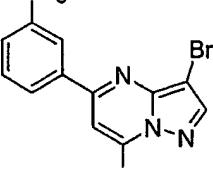
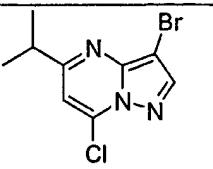
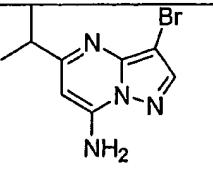
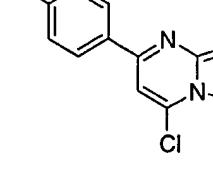
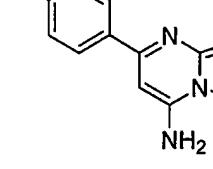
LCMS: M<sup>+</sup>=289.

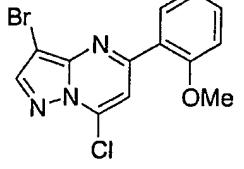
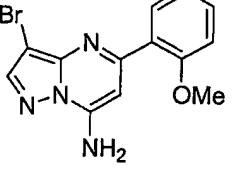
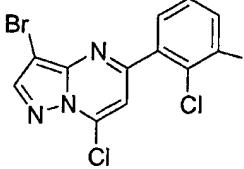
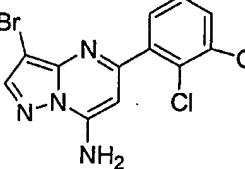
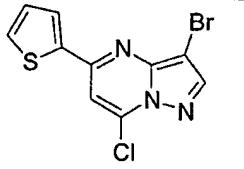
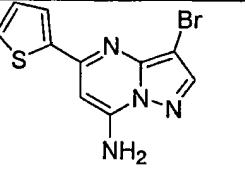
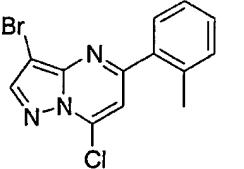
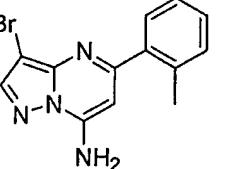
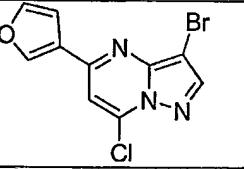
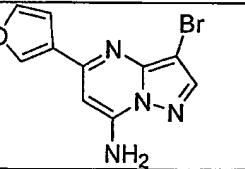
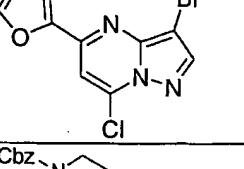
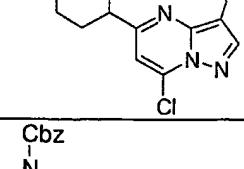
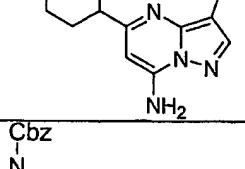
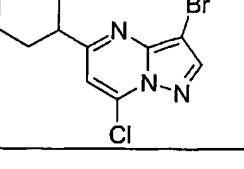
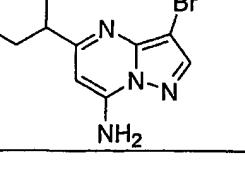
PREPARATIVE EXAMPLES 75-90:

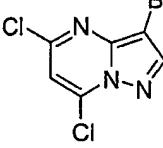
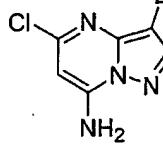
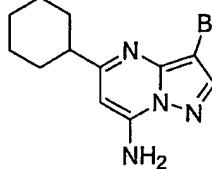
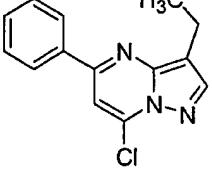
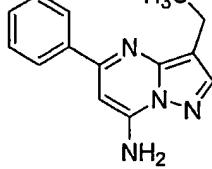
By essentially the same procedure set forth in Preparative Example 74

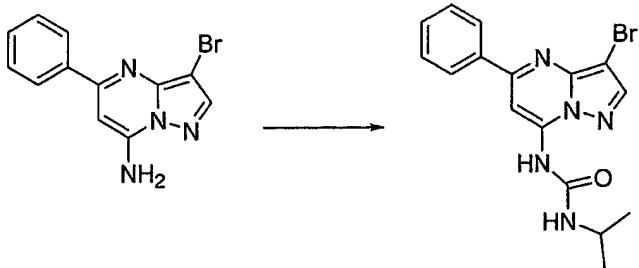
5 only substituting the compound shown in Column 2 of Table 8.10, the compounds shown in Column 3 of Table 8.10 are prepared.

TABLE 8.10

Prep. Ex.	Column 2	Column 2
75		
76		
77		
78		
79		

80		
81		
82		
83		
84		
85		
86		
87		

88		
89		
90		

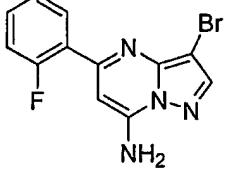
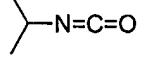
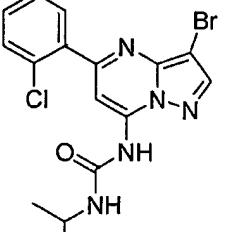
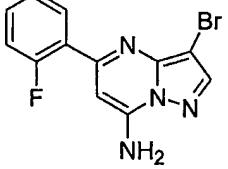
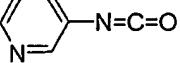
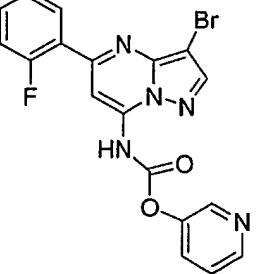
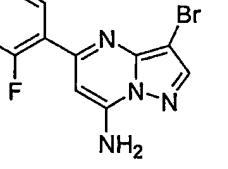
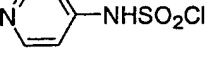
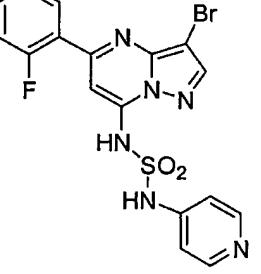
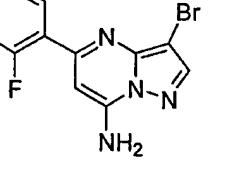
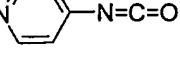
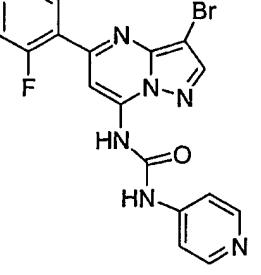
**EXAMPLE 1:**

5 To a solution of the compound prepared in Preparative Example 74 (15mg, 0.05 mmol) compound in DMF (2 mL) was added DMAP (1.0 mg), and isopropylisocyanate (30  $\mu$ L). The reaction mixture was heated at 60 °C for 20 h, cooled to rt and partitioned between EtOAc (20 mL) and H<sub>2</sub>O (20 mL). The organic layer was removed, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the product as a film. The film was purified by reversed phase HPLC to give the final product as a colorless solid. MS: m/z = 289.1

10 Examples 2 – 13:

By using essentially the same procedure set forth in **Example 1**, only substituting the amines in Column 2 of Table 9, and a suitable acylating or sulfonating agent, some illustrations being specified in column 3 of Table 9, the compounds disclosed in this invention can be prepared, some illustrations being specified in column 4 of Table 9.

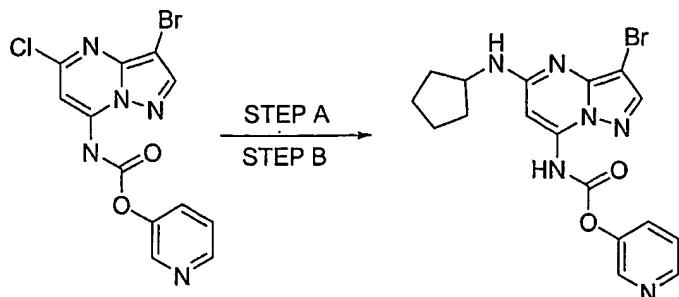
Table 9

Ex.	Column 2	Column3	Column4
2			 ms: m/z = 323.1
3			
4			
5			

6			
7			
8			
9			

10			
11			
12			
13			

**EXAMPLE 14:**

**STEP A:**

To a solution the compound prepared in Example 9 in dioxane/DIPEA

5 (2.5/1.0) at rt is added cyclopentylamine (1.2 eq.) dropwise. The resulting solution is stirred at reflux for 16h, cooled to rt, and concentrated under reduced pressure. The crude material is purified by preparative thin-layer chromatography (8 x 1000 uM).

**10 STEP B:**

To a solution of the compound prepared in Example 14, Step A in  $\text{CH}_2\text{Cl}_2$  at rt is added TFA (5 eq.) dropwise. The resulting solution is stirred for 18 h at rt and is concentrated under reduced pressure. The crude material is redissolved in  $\text{CH}_2\text{Cl}_2$  and the organic layer is sequentially washed with sat. aq.  $\text{NaHCO}_3$  (2 x 2 mL) and brine (1 x 2 mL). The organic layer is dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated under reduced pressure. The crude material is purified by preparative thin-layer chromatography (8 x 1000 uM).

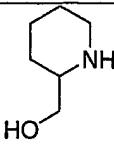
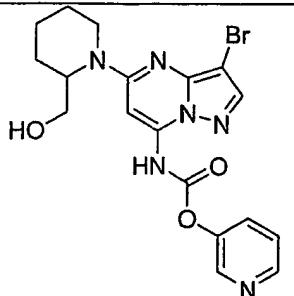
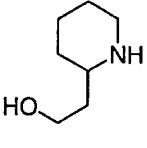
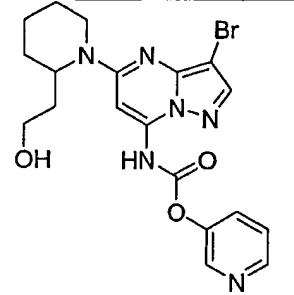
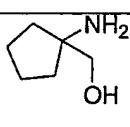
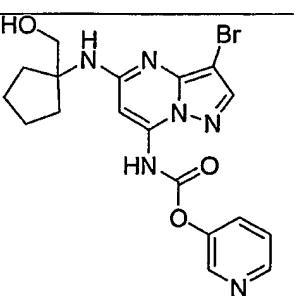
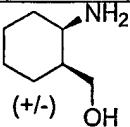
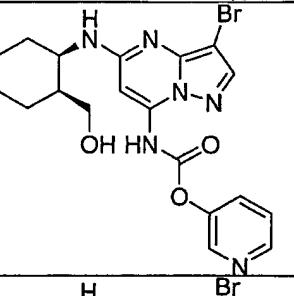
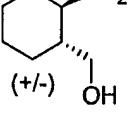
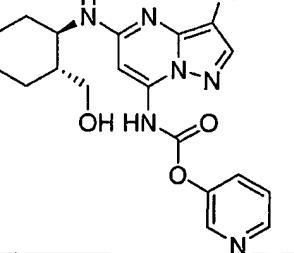
**EXAMPLES 15-24:**

By essentially the same procedure set forth in Example 48 only 20 substituting the chlorides in Column 2 of Table 10 the compounds shown in Column 3 of Table 10 are prepared.

**Table 10**

Ex.	Column 2	Column 4
-----	----------	----------

15		
16		
17		
18		
19		

20		
21		
22		
23		
24		

**ASSAY:** The assay on the compounds disclosed in the present invention can be performed by methods known to those skilled in the art. The following is a representative assay:

**BACULOVIRUS CONSTRUCTIONS:** Cyclin E is cloned into pVL1393 (Pharmingen, La Jolla, California) by PCR, with the addition of 5 histidine residues at the amino-terminal end to allow purification on nickel resin. The expressed protein is approximately 45kDa. CDK2 is cloned into pVL1393 by PCR, with the addition of a haemagglutinin epitope tag at the carboxy-terminal end (YDVPDYAS). The expressed protein is approximately 34kDa in size.

**ENZYME PRODUCTION:** Recombinant baculoviruses expressing cyclin E and CDK2 are co-infected into SF9 cells at an equal multiplicity of infection (MOI=5), for 48 hrs. Cells are harvested by centrifugation at 1000 RPM for 10 minutes, then pellets lysed on ice for 30 minutes in five times the pellet volume of lysis buffer containing 50mM Tris pH 8.0, 150mM NaCl, 1% NP40, 1mM DTT and protease inhibitors (Roche Diagnostics GmbH, Mannheim, Germany). Lysates are spun down at 15000 RPM for 10 minutes and the supernatant retained. 5ml of nickel beads (for one liter of SF9 cells) are washed three times in lysis buffer (Qiagen GmbH, Germany). Imidazole is added to the baculovirus supernatant to a final concentration of 20mM, then incubated with the nickel beads for 45 minutes at 4° C. Proteins are eluted with lysis buffer containing 250mM imidazole. Eluate is dialyzed overnight in 2 liters of kinase buffer containing 50mM Tris pH 8.0, 1mM DTT, 10mM MgCl<sub>2</sub>, 100uM sodium orthovanadate and 20% glycerol. Enzyme is stored in aliquots at -70° C.

**IN VITRO KINASE ASSAY:** Cyclin E/CDK2 kinase assays are performed in low protein binding 96-well plates (Corning Inc, Corning, New York). Enzyme is diluted to a final concentration of 50 µg/ml in kinase buffer containing 50mM Tris pH 8.0, 10mM MgCl<sub>2</sub>, 1mM DTT, and 0.1mM sodium orthovanadate. The substrate used in these reactions is a biotinylated peptide derived from Histone H1 (from Amersham, UK). The substrate is thawed on ice and diluted to 2 µM in kinase buffer. Compounds are diluted in 10%DMSO to desirable concentrations. For each kinase reaction, 20 µl of the 50 µg/ml

enzyme solution (1  $\mu$ g of enzyme) and 20  $\mu$ l of the 2  $\mu$ M substrate solution are mixed, then combined with 10  $\mu$ l of diluted compound in each well for testing. The kinase reaction is started by addition of 50  $\mu$ l of 2  $\mu$ M ATP and 0.1  $\mu$ Ci of 33P-ATP (from Amersham, UK). The reaction is allowed to run for 1 hour at 5 room temperature. The reaction is stopped by adding 200  $\mu$ l of stop buffer containing 0.1% Triton X-100, 1mM ATP, 5mM EDTA, and 5 mg/ml streptavidine coated SPA beads (from Amersham, UK) for 15 minutes. The SPA beads are then captured onto a 96-well GF/B filter plate (Packard/Perkin Elmer Life Sciences) using a Filtermate universal harvester (Packard/Perkin Elmer Life Sciences.). Non-specific signals are eliminated by washing the beads twice with 2M NaCl then twice with 2 M NaCl with 1% phosphoric acid. The radioactive signal is then measured using a TopCount 96 well liquid scintillation counter (from Packard/Perkin Elmer Life Sciences).

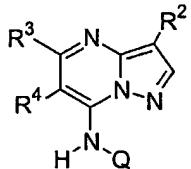
10 IC<sub>50</sub> DETERMINATION: Dose-response curves are plotted from inhibition data generated, each in duplicate, from 8 point serial dilutions of inhibitory compounds. Concentration of compound is plotted against % kinase activity, calculated by CPM of treated samples divided by CPM of untreated samples. To generate IC<sub>50</sub> values, the dose-response curves are then fitted to a standard sigmoidal curve and IC<sub>50</sub> values are derived by nonlinear regression analysis.

15 20 While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

CLAIMS

What is claimed is:

1. A compound represented by the structural formula:



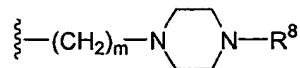
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Formula III

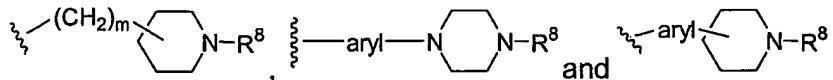
wherein:

Q is selected from the group consisting of  $-S(O_2)NR^6R^7$ ,  $-C(O)NR^6R^7$  and  $-C(O)OR^7$ ;

10  $R^2$  is selected from the group consisting of  $R^9$ , alkyl, alkynyl, alkynylalkyl, cycloalkyl,  $-CF_3$ ,  $-C(O_2)R^6$ , aryl, arylalkyl, heteroarylalkyl, heterocyclyl, alkyl substituted with 1-6  $R^9$  groups which can be the same or different and are independently selected from the list of  $R^9$  shown later below,

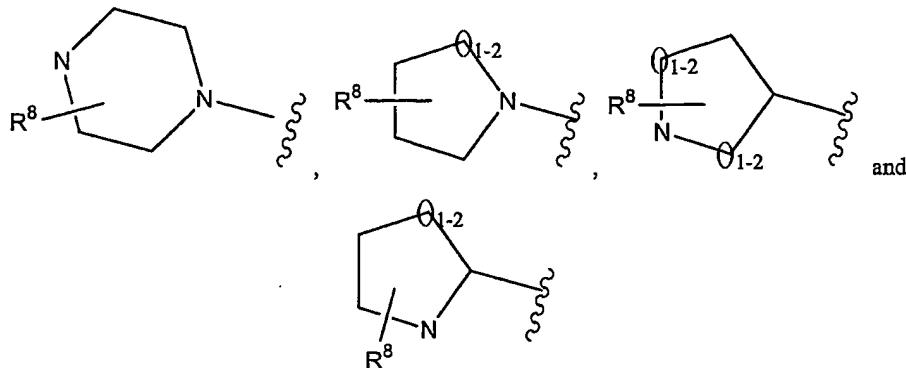


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20 wherein the aryl in the above-noted definitions for  $R^2$  can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, CN,  $-OR^5$ ,  $SR^5$ ,  $-S(O_2)R^6$ ,  $-S(O_2)NR^5R^6$ ,  $-NR^5R^6$ ,  $-C(O)NR^5R^6$ ,  $CF_3$ , alkyl, aryl and  $OCF_3$ ;

$R^3$  is selected from the group consisting of H, halogen, alkyl, alkynyl,  $-C(O)NR^5R^6$ ,  $-C(O)OR^4$ ,  $-NR^5R^6$ , cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl,



wherein each of said alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl for  $R^3$  and the heterocyclyl

5 moieties whose structures are shown immediately above for  $R^3$  can be substituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl,  $CF_3$ ,  $CN$ ,  $-OCF_3$ ,  $-(CR^4R^5)_nOR^5$ ,  $-OR^5$ ,  $-NR^5R^6$ ,  $-(CR^4R^5)_nNR^5R^6$ ,  $-C(O_2)R^5$ ,  $-C(O)R^5$ ,  $-C(O)NR^5R^6$ ,  
10  $-SR^6$ ,  $-S(O_2)R^6$ ,  $-S(O_2)NR^5R^6$ ,  $-N(R^5)S(O_2)R^7$ ,  $-N(R^5)C(O)R^7$  and  $-N(R^5)C(O)NR^5R^6$ ;

$R^4$  is H, halo or alkyl;

$R^5$  is H or alkyl;

$R^6$  is selected from the group consisting of H, alkyl, aryl, arylalkyl,

15 cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl, wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of  
20 halogen, alkyl, aryl, cycloalkyl, heterocyclylalkyl,  $CF_3$ ,  $OCF_3$ ,  $CN$ ,  $-OR^5$ ,  $-NR^5R^{10}$ ,  $-N(R^5)Boc$ ,  $-(CR^4R^5)_nOR^5$ ,  $-C(O_2)R^5$ ,  $-C(O)R^5$ ,  $-C(O)NR^5R^{10}$ ,  $-SO_3H$ ,  $-SR^{10}$ ,  $-S(O_2)R^7$ ,  $-S(O_2)NR^5R^{10}$ ,  $-N(R^5)S(O_2)R^7$ ,  $-N(R^5)C(O)R^7$  and  $-N(R^5)C(O)NR^5R^{10}$ ;

$R^{10}$  is selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl,

25 wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl can be unsubstituted or

optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, heterocyclalkyl,  $\text{CF}_3$ ,  $\text{OCF}_3$ , CN,  $-\text{OR}^5$ ,  $-\text{NR}^4\text{R}^5$ ,  $-\text{N}(\text{R}^5)\text{Boc}$ ,  $-(\text{CR}^4\text{R}^5)_n\text{OR}^5$ ,  $-\text{C}(\text{O}_2)\text{R}^5$ ,  $-\text{C}(\text{O})\text{NR}^4\text{R}^5$ ,  $-\text{C}(\text{O})\text{R}^5$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{SR}^5$ ,

5  $-\text{S}(\text{O}_2)\text{R}^7$ ,  $-\text{S}(\text{O}_2)\text{NR}^4\text{R}^5$ ,  $-\text{N}(\text{R}^5)\text{S}(\text{O}_2)\text{R}^7$ ,  $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{R}^7$  and  $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{NR}^4\text{R}^5$ ;

or optionally (i)  $\text{R}^5$  and  $\text{R}^{10}$  in the moiety  $-\text{NR}^5\text{R}^{10}$ , or (ii)  $\text{R}^5$  and  $\text{R}^6$  in the moiety  $-\text{NR}^5\text{R}^6$ , may be joined together to form a cycloalkyl or heterocyclalkyl moiety, with each of said cycloalkyl or heterocyclalkyl moiety being unsubstituted or optionally independently being substituted with one or more  $\text{R}^9$  groups;

10  $\text{R}^7$  is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, cycloalkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of

15 halogen, alkyl, aryl, cycloalkyl,  $\text{CF}_3$ ,  $\text{OCF}_3$ , CN,  $-\text{OR}^5$ ,  $-\text{NR}^5\text{R}^{10}$ ,  $-\text{CH}_2\text{OR}^5$ ,  $-\text{C}(\text{O}_2)\text{R}^5$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{10}$ ,  $-\text{C}(\text{O})\text{R}^5$ ,  $-\text{SR}^{10}$ ,  $-\text{S}(\text{O}_2)\text{R}^{10}$ ,  $-\text{S}(\text{O}_2)\text{NR}^5\text{R}^{10}$ ,  $-\text{N}(\text{R}^5)\text{S}(\text{O}_2)\text{R}^{10}$ ,  $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{R}^{10}$  and  $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{NR}^5\text{R}^{10}$ ;

$\text{R}^8$  is selected from the group consisting of  $\text{R}^6$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{10}$ ,  $-\text{S}(\text{O}_2)\text{NR}^5\text{R}^{10}$ ,  $-\text{C}(\text{O})\text{R}^7$  and  $-\text{S}(\text{O}_2)\text{R}^7$ ;

20  $\text{R}^9$  is selected from the group consisting of halogen, CN,  $-\text{NR}^5\text{R}^{10}$ ,  $-\text{C}(\text{O}_2)\text{R}^6$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^{10}$ ,  $-\text{OR}^6$ ,  $-\text{SR}^6$ ,  $-\text{S}(\text{O}_2)\text{R}^7$ ,  $-\text{S}(\text{O}_2)\text{NR}^5\text{R}^{10}$ ,  $-\text{N}(\text{R}^5)\text{S}(\text{O}_2)\text{R}^7$ ,  $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{R}^7$  and  $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{NR}^5\text{R}^{10}$ ;

$\text{m}$  is 0 to 4, and

$\text{n}$  is 1 to 4.

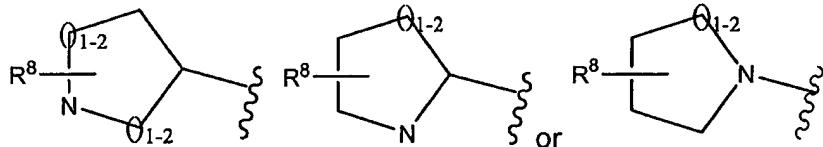
25 2. The compound of claim 1, wherein  $\text{R}^6$  is H and  $\text{R}^7$  is unsubstituted aryl, unsubstituted heteroaryl, aryl substituted with 1-3 moieties (which moieties can be the same or different with each moiety being independently selected from the group consisting of phenyl, pyridyl, thiophenyl, halogen, cyano,  $-\text{OR}^5$ ,  $-\text{S}(\text{O}_2)\text{R}^6$ ,  $\text{CF}_3$ , alkyl and  $-\text{OCF}_3$ ), and heteroaryl substituted with 1-3 moieties aryl fused

30 with an aryl or heteroaryl group (which aryl or heteroaryl may be unsubstituted or optionally substituted with 1-3 moieties which moieties can be the same or

different with each moiety being independently selected from the group consisting of phenyl, pyridyl, thiophenyl, furanyl and thiazolyl, halogen, cyano, -OR<sup>5</sup>, -SR<sup>5</sup>, -S(O<sub>2</sub>)R<sup>6</sup>, -S(O<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>, -NR<sup>5</sup>R<sup>6</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, CF<sub>3</sub>, alkyl and -OCF<sub>3</sub>);

5 R<sup>2</sup> is halogen, CF<sub>3</sub>, CN, lower alkyl, -CH<sub>2</sub>-OR<sup>6</sup>, -OR<sup>6</sup>, cycloalkyl, aryl or heteroaryl; and

R<sup>3</sup> is H, halogen, lower alkyl, aryl, heteroaryl, -C(O)OR<sup>4</sup>, cycloalkyl, -NR<sup>5</sup>R<sup>6</sup>, heterocyclalkyl,

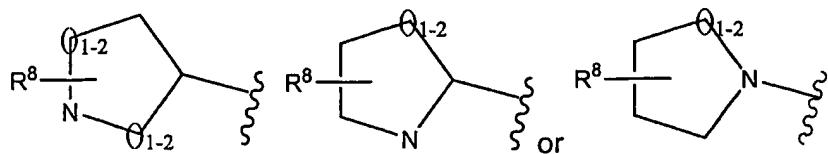


10 wherein each of said alkyl, aryl, heteroaryl, heterocycl and cycloalkyl for R<sup>3</sup> are unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, CF<sub>3</sub>, OCF<sub>3</sub>, lower alkyl, CN and OR<sup>5</sup>.

3. The compound of claim 1, wherein R<sup>10</sup> is H and R<sup>7</sup> is unsubstituted aryl, 15 unsubstituted heteroaryl, aryl substituted with 1-3 moieties (which moieties can be the same or different with each moiety being independently selected from the group consisting of phenyl, pyridyl, thiophenyl, halogen, cyano, -OR<sup>5</sup>, -S(O<sub>2</sub>)R<sup>6</sup>, CF<sub>3</sub>, alkyl and -OCF<sub>3</sub>), and heteroaryl substituted with 1-3 moieties aryl fused with an aryl or heteroaryl group (which aryl or heteroaryl may be unsubstituted or 20 optionally substituted with 1-3 moieties which moieties can be the same or different with each moiety being independently selected from the group consisting of phenyl, pyridyl, thiophenyl, furanyl and thiazolyl, halogen, cyano, -OR<sup>5</sup>, -SR<sup>5</sup>, -S(O<sub>2</sub>)R<sup>6</sup>, -S(O<sub>2</sub>)NR<sup>5</sup>R<sup>6</sup>, -NR<sup>5</sup>R<sup>6</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, CF<sub>3</sub>, alkyl and -OCF<sub>3</sub>);

25 R<sup>2</sup> is halogen, CF<sub>3</sub>, CN, lower alkyl, -CH<sub>2</sub>-OR<sup>6</sup>, -OR<sup>6</sup>, cycloalkyl, aryl or heteroaryl; and

R<sup>3</sup> is H, halogen, lower alkyl, aryl, heteroaryl, -C(O)OR<sup>4</sup>, cycloalkyl, -NR<sup>5</sup>R<sup>6</sup>, heterocyclalkyl, cycloalkylalkyl,



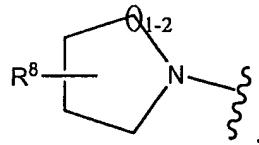
wherein each of said alkyl, aryl, heteroaryl, heterocycl and cycloalkyl for R<sup>3</sup> are unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected

5 from the group consisting of halogen, CF<sub>3</sub>, OCF<sub>3</sub>, lower alkyl, CN and OR<sup>5</sup>.

4. The compound of claim 2, wherein R<sup>2</sup> is halogen, -CH<sub>2</sub>OR<sup>6</sup>, CN, CF<sub>3</sub>, lower alkyl, cyclopropyl, C(O)OR<sup>6</sup>, -OR<sup>6</sup>, or aryl.

5. The compound of claim 2, wherein R<sup>3</sup> is H, lower alkyl, cycloalkyl, -

C(O)OR<sup>4</sup>, aryl, heteroaryl, cycloalkylalkyl,



10

wherein each of said alkyl, aryl, cycloalkyl, heteroaryl, and the heterocycl moieties shown above for R<sup>3</sup> are optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, CF<sub>3</sub>, lower alkyl,

15 OMe, aryl, cyclopropyl, and CN.

6. The compound of claim 2, wherein R<sup>4</sup> is H.

7. The compound of claim 2, wherein R<sup>5</sup> is H.

8. The compound of claim 2, wherein R<sup>6</sup> is H and R<sup>7</sup> is unsubstituted aryl.

9. The compound of claim 2, wherein R<sup>6</sup> is H and R<sup>7</sup> is unsubstituted

20 heteroaryl.

10. The compound of claim 9, wherein R<sup>7</sup> is 4-pyridyl.

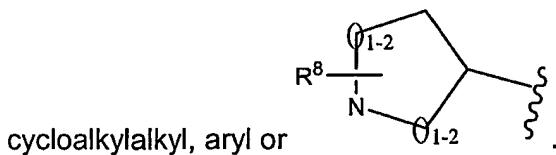
11. The compound of claim 2, wherein R<sup>7</sup> is 4-pyridyl-N-oxide.

12. The compound of claim 2, wherein R<sup>7</sup> is 4-pyridyl and Q is -SO<sub>2</sub>-NHR<sup>7</sup>.

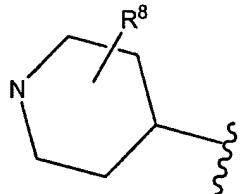
13. The compound of claim 2, wherein R<sup>7</sup> is 4-pyridyl-N-oxide and Q is

-C(O)-NHR<sup>7</sup>.

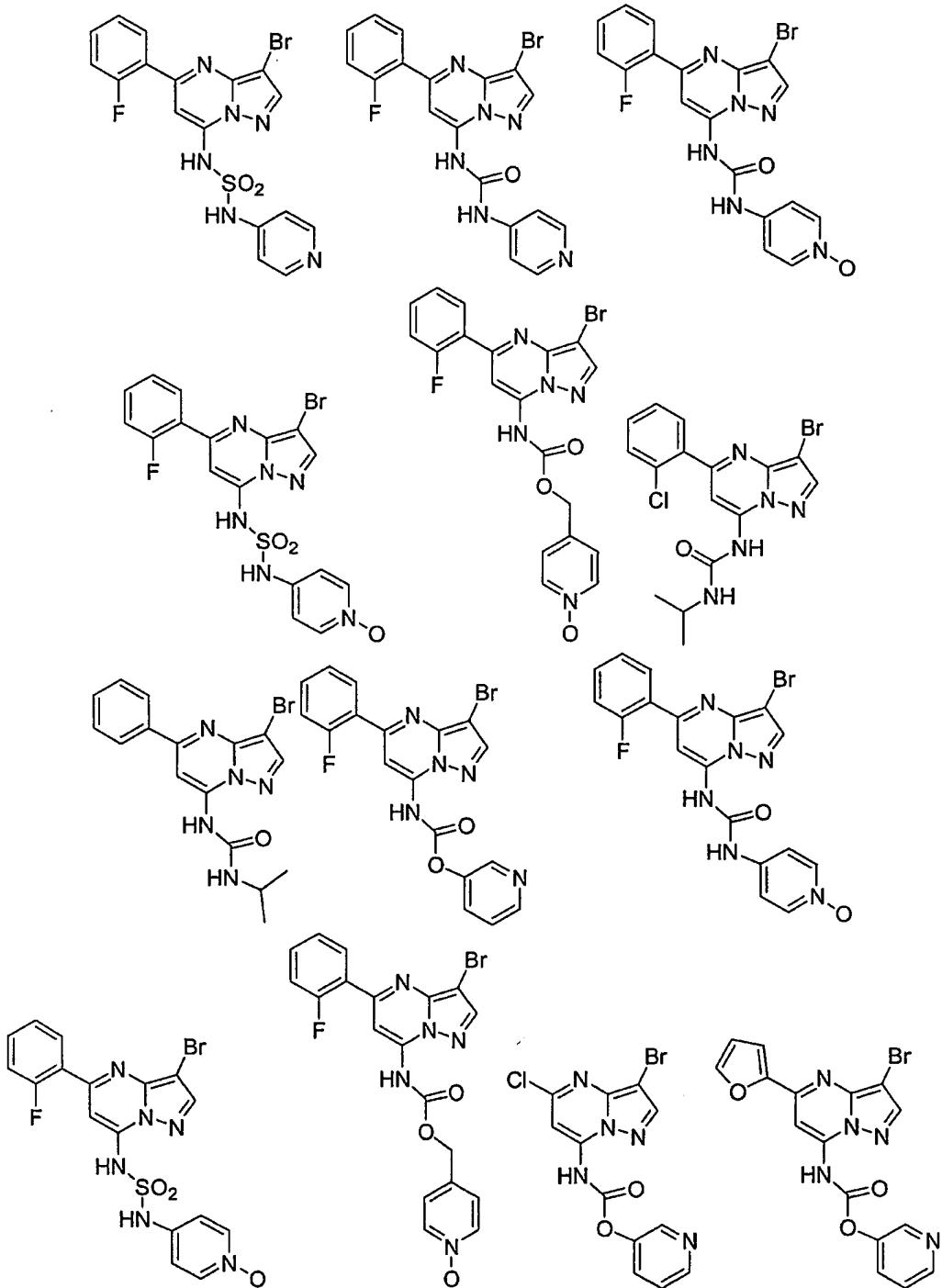
14. The compound of claim 3, wherein said R<sup>2</sup> is Br.
15. The compound of claim 3, wherein said R<sup>2</sup> is Cl.
16. The compound of claim 3, wherein R<sup>2</sup> is isopropyl or ethyl.
- 5 17. The compound of claim 3, wherein R<sup>2</sup> is -CH<sub>2</sub>OH or -CH<sub>2</sub>OCH<sub>3</sub>.
18. The compound of claim 3, wherein R<sup>2</sup> is cyclopropyl.
19. The compound of claim 3, wherein R<sup>2</sup> is CN.
20. The compound of claim 5, wherein R<sup>3</sup> is lower alkyl, cycloalkyl,



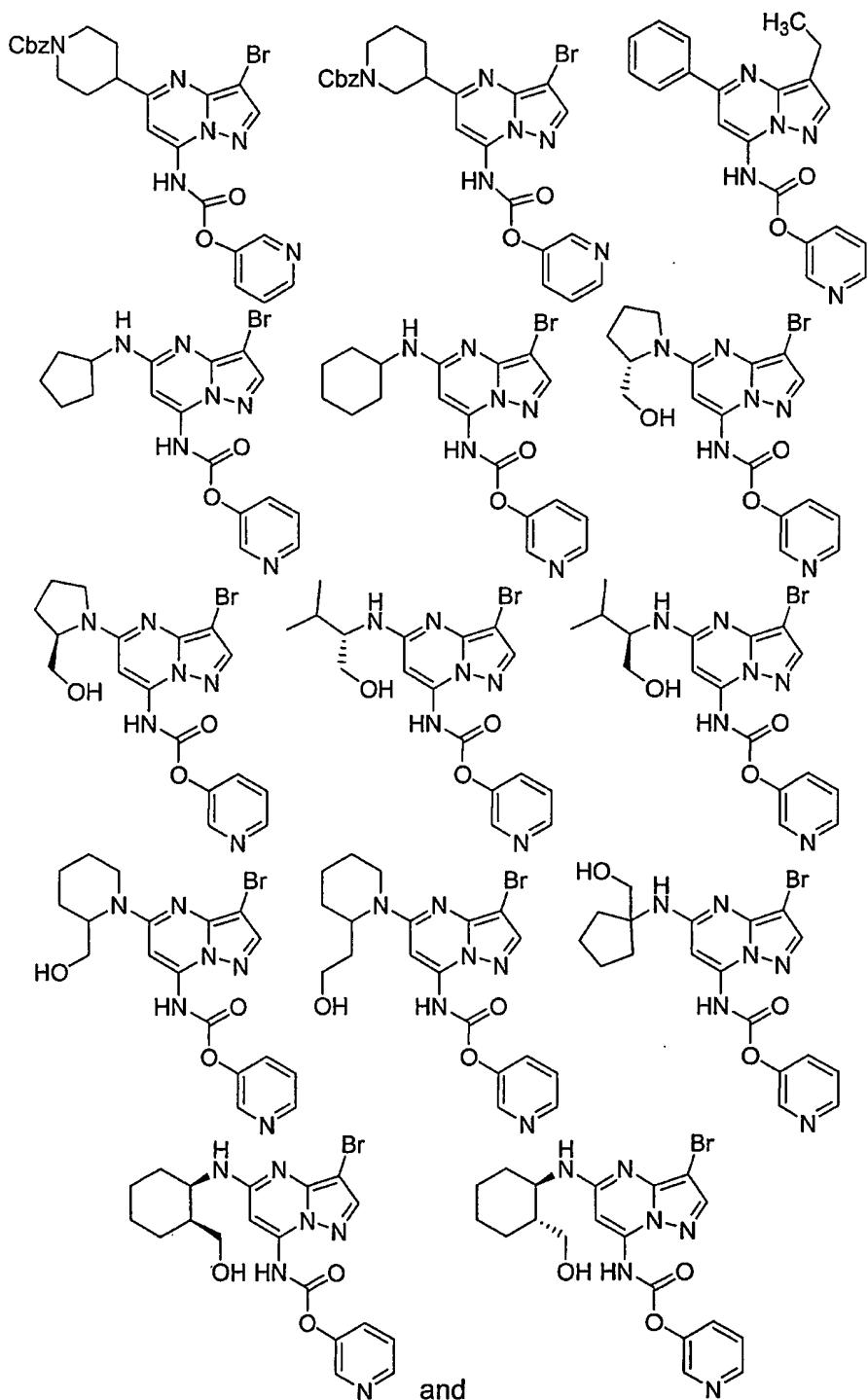
- 10 21. The compound of claim 20, wherein R<sup>3</sup> is isopropyl.
22. The compound of claim 20, wherein R<sup>3</sup> is:



23. The compound of claim 20, wherein R<sup>3</sup> is unsubstituted phenyl.
24. The compound of claim 5, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>n</sub>OH or -(CH<sub>2</sub>)<sub>n</sub>OCH<sub>3</sub>,
- 15 where n is 1 or 2.
25. The compound of claim 20, wherein R<sup>3</sup> is a phenyl substituted with one or moieties selected from the group consisting of F, Br, Cl, lower alkyl, alkoxy and CF<sub>3</sub>.
26. A compound selected from the group consisting of:



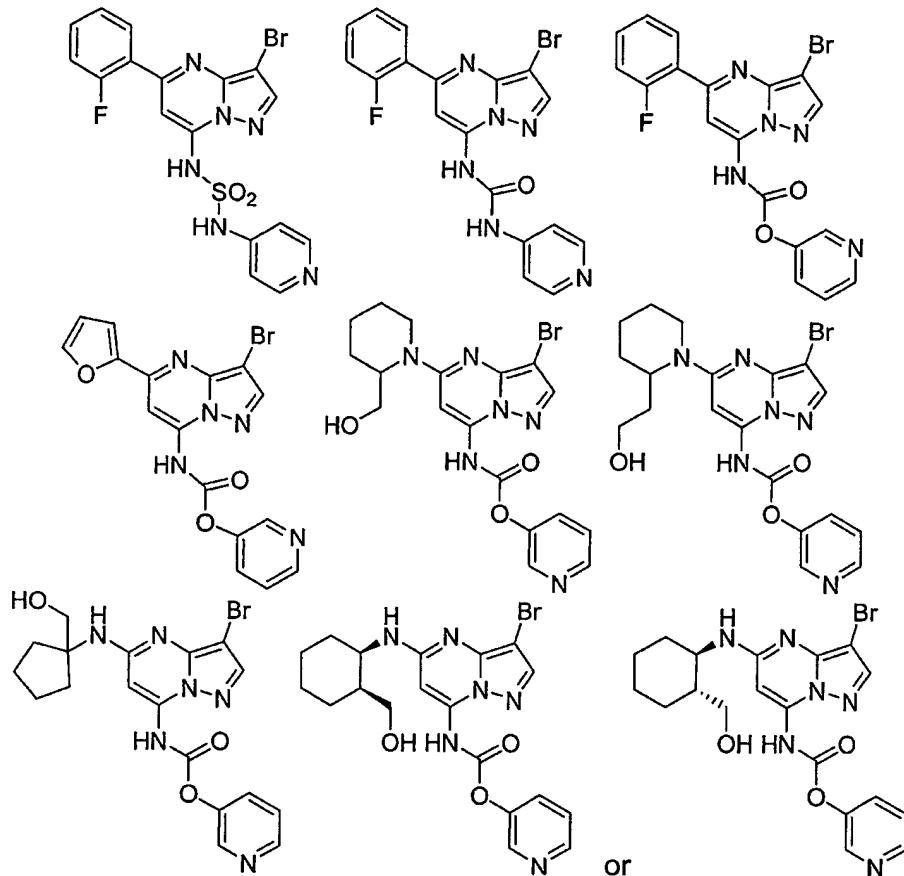
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or a pharmaceutically acceptable salt or solvate thereof.

27. A compound of the formula:



5 or a pharmaceutically acceptable salt or solvate thereof.

28. A method of inhibiting one or more cyclin dependent kinases, comprising administering a therapeutically effective amount of at least one compound of claim 1 to a patient in need of such inhibition.

29. A method of treating one or more diseases associated with cyclin

10 dependent kinase, comprising administering a therapeutically effective amount of at least one compound of claim 1 to a patient in need of such treatment.

30. The method of claim 29, wherein said cyclin dependent kinase is CDK2.

31. The method of claim 29, wherein said disease is selected from the group consisting of: cancer of the bladder, breast, colon, kidney, liver, lung, small cell

15 lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, squamous cell carcinoma; leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T- cell lymphoma,

Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, Burkett's lymphoma; acute and chronic myelogenous leukemia, myelodysplastic syndrome, promyelocytic leukemia; fibrosarcoma, rhabdomyosarcoma; astrocytoma, neuroblastoma, glioma and schwannomas; melanoma, seminoma,

5 teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoanthoma, thyroid follicular cancer and Kaposi's sarcoma.

32. A method of treating one or more diseases associated with cyclin dependent kinase, comprising administering to a mammal in need of such treatment

10 an amount of a first compound, which is a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof;  
and

an amount of at least one second compound, said second compound being an anti-cancer agent;

15 wherein the amounts of the first compound and said second compound result in a therapeutic effect.

33. The method of claim 32, further comprising radiation therapy.

34. The method of claim 32, wherein said anti-cancer agent is selected from the group consisting of a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan (or CPT-11), camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methotrexate, 5-Fluorouracil, temozolomide, cyclophosphamide, 4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide, tipifarnib, L778,123 (a farnesyl protein transferase inhibitor), BMS 214662 (a farnesyl protein transferase inhibitor), Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 30 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, oxaliplatin, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin,

Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17 $\alpha$ -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate,

5 Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine,

10 Reloxafine, Droloxafine, or Hexamethylmelamine.

35. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 1 in combination with at least one pharmaceutically acceptable carrier.

36. The pharmaceutical composition of claim 35, additionally comprising one

15 or more anti-cancer agents selected from the group consisting of cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, CPT-11, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methotrexate, 5-fluorouracil, temozolomide, cyclophosphamide, 4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide, Zarnestra<sup>®</sup> (tipifarnib), L778,123 (a farnesyl protein transferase inhibitor), BMS 214662 (a farnesyl protein transferase inhibitor), Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman,

20 25 Triethylenemelamine, Triethylenethiophosphoramide, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C,

30 L-Asparaginase, Teniposide 17 $\alpha$ -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate,

Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea,

5 Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine.

37. A compound of claim 1, in isolated and purified form.

# INTERNATIONAL SEARCH REPORT

Intern | Application No  
PCT, 03/27564

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K31/50 A61P35/00 C07D487/04 // (C07D487/04, 239:00, 231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02 50079 A (ULIBARRI GERARD ; LONCHAMPT MARIE-ODILE (FR); THURIEAU CHRISTOPHE () 27 June 2002 (2002-06-27) page 5, line 22 -page 7, line 12; claim 1 -----	1-37
A	EP 1 199 306 A (BANYU PHARMA CO LTD) 24 April 2002 (2002-04-24) page 4, line 7 -page 8, line 30 ----- -/-	1-37

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

\*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the International search report
12 December 2003	22/12/2003

Name and mailing address of the ISA  
 European Patent Office, P.B. 5818, P.O. Box 2  
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Authorized officer

Wörth, C

## INTERNATIONAL SEARCH REPORT

Inter	Application No
PC	03/27564

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SENDEROWICZ A M ET AL: "PRECLINICAL AND CLINICAL DEVELOPMENT OF CYCLIN-DEPENDENT KINASE MODULATORS" JOURNAL OF THE NATIONAL CANCER INSTITUTE, US DEPT. OF HEALTH, EDUCATION AND WELFARE, PUBLIC HEALTH, US, vol. 92, no. 5, 1 March 2000 (2000-03-01), pages 376-387, XP001097834 ISSN: 0027-8874 figure 4 ---	1-37
A	HONMA TERUKI ET AL: "Structure-Based Generation of a New Class of Potent Cdk4 Inhibitors: New de Novo Design Strategy and Library Design" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 44, 2001, pages 4615-4627, XP002220243 ISSN: 0022-2623 example 14A; table 2 ---	1-37
A	EP 0 714 898 A (OTSUKA PHARMA CO LTD) 5 June 1996 (1996-06-05) cited in the application claim 1 ---	1-37

## INTERNATIONAL SEARCH REPORT

Int'l application No.  
PCT/US 03/27564

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 28-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple Inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

Inten	Application No
PCT/US 03/27564	

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WO 0250079	A	27-06-2002		FR 2818278 A1 AU 2509602 A CA 2432417 A1 EP 1345941 A1 WO 0250079 A1		21-06-2002 01-07-2002 27-06-2002 24-09-2003 27-06-2002
EP 1199306	A	24-04-2002		AU 6314900 A CA 2380389 A1 EP 1199306 A1 WO 0107411 A1 JP 2001106673 A		13-02-2001 01-02-2001 24-04-2002 01-02-2001 17-04-2001
EP 0714898	A	05-06-1996		AT 208776 T AU 680370 B2 AU 2576595 A CA 2169719 A1 DE 69523864 D1 DE 69523864 T2 DK 714898 T3 EP 0714898 A1 US 5707997 A CN 1131948 A ,B ES 2164153 T3 WO 9535298 A1 JP 3163412 B2 JP 8311068 A JP 3163413 B2 JP 8310951 A PT 714898 T		15-11-2001 24-07-1997 15-01-1996 28-12-1995 20-12-2001 13-06-2002 18-03-2002 05-06-1996 13-01-1998 25-09-1996 16-02-2002 28-12-1995 08-05-2001 26-11-1996 08-05-2001 26-11-1996 29-04-2002